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VOLUME 50 NUMBER 4

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ARCHIVES OF SURGERY

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PROPHYLAXIS OF WOUND INFECTION

STUDIES WITH PARTICULAR REFERENCE TO SOAPS AND IRRIGATION

L. W. PETERSON, M.D.

CHICAGO

Since the time of Lister, the local care given wounds—particularly from the standpoint of prophylaxis of infection—has been the center of much medical discussion. Naturally, the type of therapy used will be influenced by such factors as the degree of contamination, the length of time since injury and the location, type and extent of injury.

Various antiseptics, as they have been discovered, have been used in wounds as easy substitutes for cleansing. It was learned long ago that antiseptics strong enough to destroy bacteria in wounds would likewise have a harmful effect on the tissues. World War I and the good results obtained by Dr. Alexis Carrel [1] in the treatment of infected wounds at his hospital at Compiègne, France, brought about a widespread acceptance of wound irrigation. After experimenting with numerous disinfectants, in conjunction with Dakin, he concluded that his best results were obtained with use of a solution of sodium hypochlorite in a concentration of between 0.45 and 0.50 per cent in irrigating contaminated wounds.

Orr,[2] in 1925, condemned both the mechanical and the chemical method of treating contaminated wounds. It was his opinion that both were irritating to the body tissues, and he advocated, instead, immobilization of the involved part.

In 1937, Mason [3] emphasized the fact that contamination is present in most wounds and stressed the importance of converting them into clean wounds. This, he believed, one could best and most easily accomplish, after first preparing the surrounding skin, by the gentle washing of the wound with soap and water followed by irrigations with isotonic solution of sodium chloride.

Four years later, Koch [4] stated that in his judgment there was no method so effective, and none which carried so little risk of injuring the exposed and vulnerable living tissues, as the use of plain white soap and sterile water. He advocated washing the wound gently but thoroughly for a period of not less than ten minutes with soap and water applied with soft cotton, followed by prolonged irrigation of the cleansed wound with warm isotonic solution of sodium chloride.

The wound toilet described by Whipple,[5] which he recommended in the treatment of accidental wounds, consisted of a complete débridement followed by a thorough irrigation of the wound with isotonic saline solution. Kerrigan [6] reported a series of 12,044 open wounds in a five year period which had been cleansed with soap and water, and he stated that his results were extremely gratifying. Estes,[7] under the heading of "Cleansing of the Wound," recommended that the wound be washed very gently with soap and water and irrigated with isotonic saline solution.

In describing the technic used in the Cincinnati General Hospital in 1941, Stevenson [8] condemned cleansing or irrigating the traumatic wounds. He stated that this is no substitute for thorough excision. Irrigating the wound, he believed, might spread contamination and transform a dirty wound into one that merely looks clean, and the surgeon might take liberties with it and not do a thorough débridement.

From the Department of Surgery, University of Illinois College of Medicine.

Dr. Milan Novak, of the Department of Bacteriology, assisted in these studies, and Mr. E. Hoppe gave technical assistance.

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2. Orr, H. W.: Mechanical vs. Chemical Methods in the Treatment of Wounds, Journal-Lancet **45**:515-518 (Nov.) 1925.

3. Mason, M. L.: The Surgical Principles Involved in the Treatment of Open Injuries, West. J. Surg. **45**: 239-248 (May) 1937.

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5. Whipple, A. O.: Essential Principles in Clean Wound Healing, Surg., Gynec. & Obst. **70**:257-260 (Feb.) 1940.

6. Kerrigan, R. L.: Exclusive Use of Soap and Water in Traumatic Wounds, Surg., Gynec. & Obst. **75**:165-169 (Aug.) 1942.

7. Estes, W. J.: Use of Antiseptics in Treatment of Open Wounds, Am. J. Surg. **47**:369-374 (Feb.) 1940.

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After studying his own results and those of other workers in the treatment of soft tissue wounds, Meleney [9] concluded that a prolonged irrigation of the wound prior to débridement increases the incidence of infection but that a short irrigation after a dry débridement may be of value.

Ives and Hirshfeld,[10] investigating the work of Hunt, found that all the clean surgical wounds that they studied were extensively contaminated with bacteria, predominantly Staphylococcus aureus. Jackson and Jackson [11] applied the work of Mason on traumatic wounds to the surgical wounds of the operating room, which Ives and Hirshfeld proved to be extensively contaminated. In a series of 200 cases, which included cases of breast amputations for carcinoma, open reductions of femur fractures and amputations at the thigh for senile gangrene, they washed the wounds with dilute green soap and water for a period of two to five minutes before closing them. They concluded that this treatment did not interfere with ideal healing of the wound but actually aided in repair, as evidenced by the absence of redness, induration and irritation.

Much has been written about the germicidal properties of soap. Walker [12] stated that pneumococci are highly susceptible to the germicidal action of soap and that streptococci are also killed by soap but that staphylococci possess more resistance to its action. In a series of experiments, Novak [13] showed dramatically the extreme effectiveness of the germicidal activity of soap against such common bacteria as hemolytic Staph. aureus, colon bacilli and the United States Government's standard strain for testing antiseptics (Staphylococcus no. 209). He found that 20 per cent green soap and 20 per cent white soap in five minutes either sterilized the cultures or reduced the number of bacteria from 25,000 per cubic centimeter to 3 or less.

Notwithstanding the fact that the germicidal property of soap is unquestionable and that the irritative quality of soap in wounds is neither great nor particularly damaging, the superiority of cleansing with soap and water over other methods of cleansing wounds has not been definitely established. Therefore, a series of experiments on animals were devised and conducted, in the hope that information relative to this problem could be obtained.

EXPERIMENTAL METHODS

In these experiments on the prophylaxis of wound infection, both clean and contaminated wounds were studied in a series of 76 dogs. The contamination was accomplished by allowing a fixed amount of culture of hemolytic Staph. aureus to remain in contact with the wounds for a period of one hour prior to therapy. The relatively short duration of the bacterial contact made these wounds more closely comparable to surgical wounds produced in the operating room than to civilian or battle injuries.

All wounds were made on the carefully shaved backs of the animals, after first preparing the skin by washing with soap and water and then painting it with iodine and removing the iodine with alcohol. Pentobarbital sodium was the drug used as the anesthetic agent in all the experiments, and it was administered intraperitoneally in a solution.

1. *Effect of Soap on the Healing of Noncontaminated Wounds.*—The first group of dogs was used to compare the irritative qualities of 20 per cent green soap, 20 per cent white (neutral) soap and the 10 per cent green soap used for scrubbing hands in the operating rooms of the Illinois Research and Educational Hospital. Four parallel incisions were made through the skin of the dog's back, each measuring 1½ inches (3.8 cm.) in length. Hemostasis was obtained as atraumatically as possible, and each of the three incisions was soaked with one of the three soaps under investigation for a period of one hour, the fourth incision being used as a control. On application of the soaps, the wounds were covered with sterile gauze to eliminate air-borne contamination. After a period of one hour, all four incisions were carefully irrigated with isotonic solution of sodium chloride. This was done by running the sterile saline solution from a flask, suspended 3 feet (0.9 meter) above the dog, through a set used for intravenous injections. The needle was removed and the glass adapter used to direct the stream of solution into the wounds. These wounds were not scrubbed and were closed immediately after the irrigations. Interrupted mattress sutures of black silk were used and were placed in such a way that they would not enter the wound space and would give the wound good approximation without penetrating the edge. Individual collodion gauze dressings were then placed over each incision.

On the fourth and seventh days after the wounds were treated with the soaps, gross observations were made and a biopsy specimen for microscopic examination was taken from each of the wounds.

During the hour period in which the wounds of this group of dogs were being soaked with the soap solutions, the conjunctival sac and cornea of one eye was kept flooded with the 20 per cent green soap and the other flooded with the 20 per cent white soap. The eyes were observed for inflammation and keratitis after one hour, after twenty-four hours and on the fourth day.

9. Meleney, F. L.: A Statistical Analysis of a Study of the Prevention of Infection in Soft Part Wounds, Compound Fractures, and Burns with Special Reference to the Sulfonamides, Surg., Gynec. & Obst. **80**:263-296 (March) 1945.

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12. Walker, J. E.: The Germicidal Properties of Chemically Pure Soaps, J. Infect. Dis. **35**:557-566 (Dec.) 1924.

13. Novak, M. V.: Personal communication to the author.

2. *Effect of Scrubbing on the Healing of Noncontaminated Wounds.*—To compare the irritation of soap and mechanical scrubbing with the irritation of the soap alone, three of incisions of the same type were made on the back of each dog. The first was washed gently with cotton and white soap for a period of ten minutes; the second, with surgical gauze dressings and white soap for the same length of time, and the third wound was prepared to be used as a control by just soaking it with the same soap for the same length of time. After ten minutes all three wounds were irrigated with isotonic solution of sodium chloride and sutured and dressed in the manner previously described. On the fourth day, the wounds were observed grossly, materials for cultures taken and the biopsy specimens taken for microscopic examination.

3. *Effect of Soap and Scrubbing on the Healing of Contaminated Wounds.*—To the wounds of the next group of dogs was added bacterial contamination. Six incisions were made on the back of each of these dogs and contaminated with 0.1 cc. of a twenty-four hour culture of hemolytic Staph. aureus. This culture contained approximately 1,100,000,000 bacteria per cubic centimeter. After the bacteria had been in the wounds for a period of one-half hour, the first wound was filled with 20 per cent green soap, the second was filled with 20 per cent white soap and the third was washed gently with a cotton applicator and white soap for a period of sixty seconds. A gauze-tipped forceps and white soap were used to wash out the fourth wound. The fifth and sixth wounds were not treated with soap. After a period of one hour, each wound except the sixth (which was used as a control wound) was irrigated thoroughly with 250 cc. of isotonic solution of sodium chloride. All wounds were then closed and observed and materials taken for cultures on the fourth postoperative day.

4. *Effect of Irrigation with Various Quantities of Isotonic Solution of Sodium Chloride on the Healing of Contaminated Wounds.*—On the back of each of the last group of dogs, four transverse incisions were made, and, after proper hemostasis, were contaminated as described previously. After a period of one hour, the first wound was irrigated with 1,000 cc. of isotonic solution of sodium chloride in the manner previously described; the second was irrigated with 500 cc. of solution, and the third, with 250 cc. of solution. The last wound was used as a control and not irrigated. The four incisions were then closed, and an individual collodion gauze dressing was placed on each. After four days, the wounds were observed and materials for cultures taken.

The technic of the bacterial examination of the wounds was as follows: After removal of the collodion gauze with the aid of ether, the incisions were painted with tincture of iodine solution. A sterile capillary Wright pipet was placed into the wound, and fluid, if present, was drawn up the tube for a distance of 1 cm. The fluid obtained in this way was then emptied into a sterile tube containing 5 cc. of warm sterile agar and then emptied into a sterile Petri dish and incubated at 37 C. for twenty-four hours. After this length of time, the number of colonies growing in each Petri dish was counted and recorded.

RESULTS OF THE EXPERIMENTS

1. *Effect of Soap on the Healing of Noncontaminated Wounds.*—As previously stated, all the wounds soaked with the 20 per cent green soap, 20 per cent white soap and 10 per cent green soap for a period of one hour and the control wounds, with no soap, were irrigated with isotonic solution of sodium chloride and then closed. Eleven dogs were used in this experiment. Most of the wounds in this group healed per primam. No difference in the amount of infection could be determined by gross examination or bacteriologic study. However, microscopically there was slightly less inflammatory cell infiltration and slightly more fibroplasia between the wound edges in the biopsy specimens taken from the control wounds. No difference could be detected microscopically between the wounds treated with 20 per cent green soap and 20 per cent white soap, but these wounds showed more inflammatory response and less fibroplasia than the wounds treated with the 10 per cent green soap.

The eyes of the dogs in this group had been flooded with soap for a period of one hour—20 per cent green soap in the left eyes and 20 per cent white soap in the right eyes. In the eyes of all the dogs, definite signs of irritation were present. The white soap formed a pseudomembrane over the cornea; however, after the eyes were washed with isotonic saline solution, the underlying signs of inflammation were approximately the same in the two eyes of each dog. The conjunctival vessels were engorged to approximately three times normal size. The corneas lost their luster, and an obvious keratitis was present one hour after the soap had been removed. This was evidenced by the whitening of the corneas, which was still present on observation on the fourth day, and no difference could be discerned between the actions of the two soaps.

2. *Effect of Scrubbing on the Healing of Noncontaminated Wounds.*—In the second experiment 6 dogs were used, and three incisions were made on the back of each dog. The first incision was washed with gauze and white soap; the second, with cotton and white soap, and the third, which was the control wound, was merely soaked with white soap for a period of ten minutes. These wounds were then irrigated with isotonic solution of sodium chloride and closed. There was a decided and consistent difference microscopically. This difference did not show grossly, for all wounds healed without gross evidence of inflammation. On the fourth postoperative day, the wounds washed with gauze exhibited microscopically the greatest amount of inflammatory cell infiltration of the wound edges and the least fibroplasia. The control wounds, which were not washed mechanically but just bathed in the soap, showed little or no inflammation microscopically

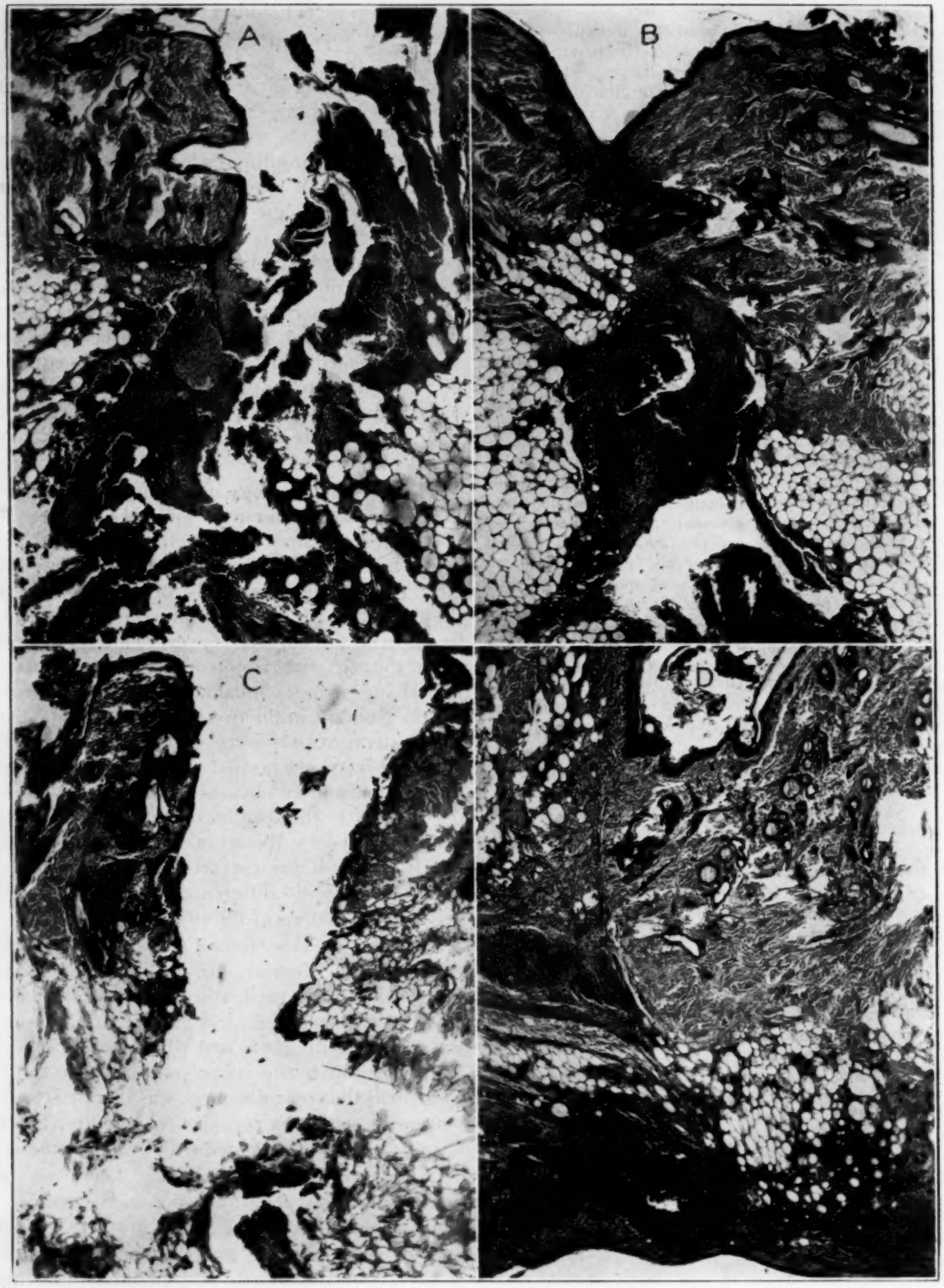

Fig. 1.—Photomicrographs of biopsy specimens taken from wounds on the seventh day after treatment. Sections *A* and *B* are from wounds treated with 20 per cent green soap and 20 per cent white soap, respectively. Both show delayed fibroplasia and a deposition of an increased number of inflammatory cells in the area. Section *C*, taken from a wound treated with 10 per cent green soap, shows much less infiltration of leukocytes but little tendency toward healing; the wound in this section was partially disrupted during the cutting of the block of tissue for section. Section *D* represents the control wound not treated with soap and shows good healing and little evidence of inflammation.

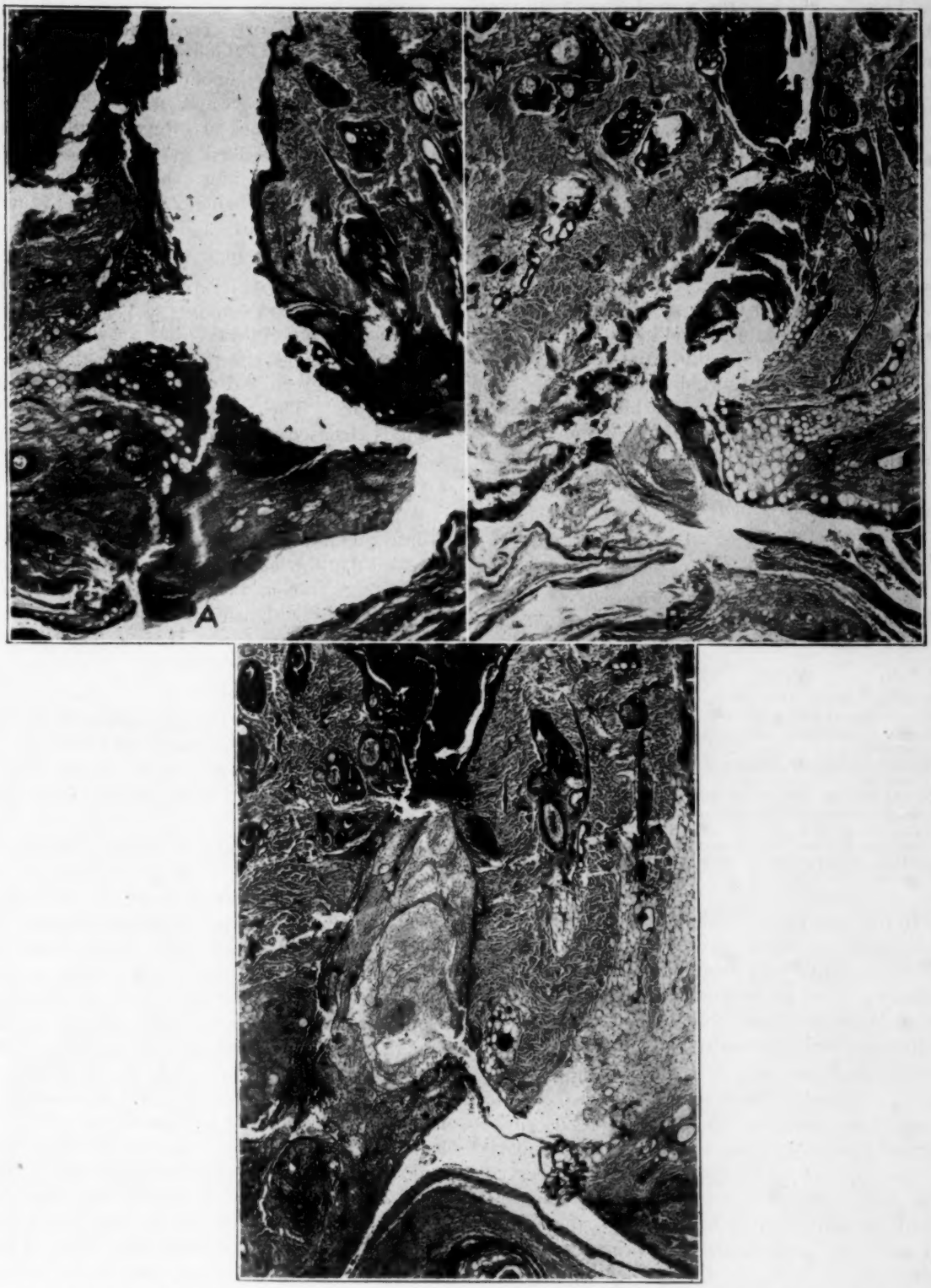

Fig. 2.—Photomicrographs of biopsy specimens taken from wounds on the fourth day after treatment. Section *A*, taken from a wound scrubbed with gauze and white soap for ten minutes, shows little evidence of fibroblastic proliferation and a large amount of inflammatory cell infiltration. Section *B*, taken from a wound scrubbed with cotton and white soap, shows less infiltration of leukocytes and many fibroblasts connecting the wound edges. The control wound, section *C*, shows a solid union of the wound edges with practically no microscopic evidence of inflammation.

and a solid union of the wound edges with fibroblasts. The wounds washed with cotton and soap for the ten minute period took the middle point microscopically, both in healing and in the inflammatory changes around the wound edges.

3. *Effect of Soap and Scrubbing on the Healing of Contaminated Wounds.*—The third series of experiments, performed on 48 dogs, added the effect of Staph. aureus contamination to the other factors already included in the previous experiments. The bacteria were left in contact with the wounds for half an hour. Twenty per cent green soap was added to the first incision and 20 per cent white soap to the second incision for a period of one-half hour. The third and fourth wounds were mechanically scrubbed with gauze and white soap, and cotton and white soap, respectively, for sixty seconds. Each of the first five incisions was then irrigated with 250 cc. of isotonic solution of sodium chloride, and the sixth wound was not treated.

TABLE 1.—*Comparison of Various Methods of Cleansing Wounds Contaminated with Hemolytic Staphylococcus Aureus*

Type of Cleansing	Average Degree of Infection *
Wounds soaked with green soap for one-half hour....	2.69
Wounds soaked with white soap for one-half hour....	2.14
Wounds washed with gauze and white soap for sixty seconds	1.66
Wounds washed with cotton and white soap for sixty seconds	1.54
Control wounds—not treated with soap or irrigation	1.43
Wounds irrigated with isotonic saline solution only...	0.38

* 0 indicates that the wound healed per primam with no infection. Infections were graded from 1 to 4, 4 representing the most severe grade.

In the analysis of results of the experiments in this series, cultures were practically useless. When any fluid was obtained from a wound, the culture yielded an innumerable quantity of colonies. When no fluid was found in a wound, the culture yielded from no colonies to six colonies.

The resultant effects of the bacteria in the various wounds treated in the described manner were, therefore, determined by the degree of infection produced. This was related particularly to the amount and type of exudate observed. The degree of infection in the wounds was arbitrarily graded from 0 to 4. When the wound appeared to have healed per primam with no collection of fluid, it was graded 0, and the wounds were graded from 1 to 4 depending on the degree of infection. This was determined by the amount of purulent fluid present in the wound and the extent of induration, redness, heat, lack of healing, etc. Table 1 summarizes the results of this experiment.

The contaminated wounds treated with white soap and green soap for one-half hour, as previously described, exhibited at the end of the fourth day greater amounts of infection than those treated in other ways. In all these wounds, large abscesses formed. However, in the wounds which had been soaked in green soap before closure, the most infection consistently developed, the average grades being 2.69 for the wounds soaked with green soap and 2.14 for the wounds soaked with white soap.

The majority of the wounds washed with gauze or cotton and soap for sixty seconds before irrigation became infected, but the degree of inflammation was less in these than in the wounds soaked with green and with white soap for one-half hour. The average grade given the wounds cleansed with gauze and white soap was 1.66. When cotton was substituted for gauze, the average was 1.54.

After computation of an average of the degree of infection in the various types of wounds, it was revealed that the least infection was present in the wounds that were not treated with soap but were only irrigated with isotonic solution of sodium chloride; this figure was 0.38, representing a minimal amount of infection.

The degree of infection of the wounds contaminated by bacteria but not subjected to any local form of treatment averaged 1.43, which compares unfavorably with that of the wounds which were contaminated and then irrigated with isotonic saline solution.

4. *Effect of Irrigation with Various Quantities of Isotonic Solution of Sodium Chloride on the Healing of Contaminated Wounds.*—When it was discovered that the wounds irrigated with isotonic saline solution healed better than any of the other wounds, including the controls, it was decided to attempt to find out whether there is an optimum amount of irrigation from the standpoint of wound healing. Accordingly, in a group of 11 dogs, four incisions were made on the prepared back of each dog, and each wound was contaminated with the standard amount of the culture of hemolytic Staph. aureus. After a period of one hour, the first wound was irrigated with 1,000 cc. of isotonic solution of sodium chloride; the second, with 500 cc. of the solution, and the third wound was irrigated with just 250 cc. of the solution. The fourth wound, which was used as a control, was not irrigated. All wounds were closed and were observed and cultures taken after four days. The wounds in this experiment were graded from 0 to 4 on each of six points, namely (1) the amount of exudate outside the wound, (2) the amount of fluid within the wound, (3)

the amount of induration of the wound, (4) the degree of wound healing, (5) the presence of stitch abscesses and (6) the amount of redness of the wound. Again, the cultures were of no value in grading the wounds; the majority of the cultures showed innumerable colonies of bacteria. The result of this experiment is summarized in table 2.

TABLE 2.—*Comparison of Wounds Contaminated with Hemolytic Staphylococcus Aureus and Cleansed with Irrigations of Various Quantities of Isotonic Solution of Sodium Chloride*

	Amount of Solution			
	Control	250 Cc.	500 Cc.	1,000 Cc.
	Grade	Grade	Grade	Grade
Exudate	1.72	1.45	0.66	0.72
Fluid within wound	1.45	0.64	0.33	0.36
Induration	1.91	0.91	0.66	0.72
Lack of healing	1.57	0.86	1.00	0.57
Stitch abscesses	1.45	1.18	1.33	1.00
Redness	0.18	0	0	0
Average *	1.38	1.00	0.79	0.67

* The wounds were graded from 0 to 4, as in table 1. Zero represents no evidence of the characteristic indicated. Maximum evidence was graded as 4.

The control wounds in this experiment, which were contaminated with bacteria but not irrigated with isotonic saline solution, were the wounds most infected. Though the wounds irrigated with 250 cc. of solution were definitely less infected than the controls, the wounds irrigated with 500 cc. of solution were even less infected, and the least infected wounds were the ones irrigated with 1,000 cc. of isotonic saline solution.

SUMMARY

There is no doubt as to the efficacy of the various soaps as germicidal agents. However, in these experiments, when the soaps were placed in actual contact with the uncontaminated fresh wounds, they produced a definite but slight irritation. This was noted only on microscopic examination; gross examination revealed no difference between control wounds and wounds into which soap had been placed. However, in wounds which were contaminated by placing a given amount of a culture of Staph. aureus within their depths and then exposed to soap, there was a definite increase in signs of infection over those found in the control wounds not exposed to soap; "green" soap was found more irritating than "white" soap.

The harmful effect of mechanical washing of the wounds is in direct proportion to the coarseness of the material used.

These experiments indicated that of the various methods studied the cleansing of contaminated wounds by a *gentle* irrigation with isotonic solution of sodium chloride is the most effective prophylaxis of wound infection. Contaminated wounds treated by this gentle irrigation healed with less evidence of infection than did control contaminated wounds subjected to no treatment other than closure at the specified time. Best results in cleansing these small wounds were obtained by irrigating them with 1,000 cc. of saline solution with no scrubbing, utilizing the force of the stream as the washing mechanism.

OSSEOUS, CARTILAGINOUS AND MIXED TUMORS OF THE HUMAN BREAST

A REVIEW OF THE LITERATURE

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During the past century an interesting literature pertaining to a group of rare tumors of the breast has developed. Collectively they are characterized by the presence of bone, cartilage, fibrous tissue and pleomorphic cells, and, depending on whether these elements are found alone or in combination, the tumors have been reported as chondroma, osteochondroma, chondrosarcoma, osteochondrosarcoma, osteosarcoma, osteoid sarcoma, giant cell sarcoma, myeloid sarcoma, mixed tumor, osteoclastoma and teratoma.

In 1700 Bonet [1] reported observing in a female breast a stony hard mass "which could not be cut with a knife." Since at this period microscopic study of tissue had not evolved and also because stony hard tumors were called bony or cartilaginous, it would be inaccurate to refer to this early contribution as the first example of the tumors under discussion. The same critical attitude must be maintained toward the bony and cartilaginous tumors reported by Morgagni,[2] Reil,[3] Cooper,[4] Warren,[5] Cruveilhier [6] and Velpeau.[7] As Foucher's [8] enchondroma arose from costal cartilages and not from mammary gland, his contribution must also be discarded. The first case of this group to be reported with microscopic study came from the pen of Lancereaux [9] in 1860. Subsequently, tumors from about 105 other cases were described. We have studied all but 8 [10] of these reports and feel that it would not be amiss to present an analysis of them.

From St. Vincent's Hospital.

1. Bonet, T.: Sepulchretum, sive anatomia practica ex cadaveribus, morbo denatis, Geneva, Cramer et Perachon, 1700, book 3, chap. 61, p. 522.
2. Morgagni, J. B.: De sedibus et causis morborum, Ebroduni in Helvetia, 1779, vol. 3, epistol. 50, obs. 41 and 43, p. 42.
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4. Cooper, A. P.: Illustrations of the Diseases of the Breast, London, Longman, Rees & Co., 1829, p. 65.
5. Warren, J. C.: Surgical Observations on Tumours, Boston, Crocker & Brewster, 1837, p. 213.
6. Cruveilhier, J.: Traité d'anatomie pathologique générale, Paris, J.-B. Baillière & fils, 1856, vol. 3, p. 824.
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ENCHONDROMA

Seven cases of enchondroma constitute this group, in all of which the tumors occurred in females from 14 to 54 years of age. The patients were cognizant of their tumors from one to thirty-two years. The tumors grew slowly and progressively in 5 patients and after a long stationary period in 1. Mastectomy was performed in 1 case, and in the remaining cases the treatment was excision. The postoperative course in all instances proved uneventful. Six months after operation a recurring tumor was removed in Cambria's case. As to the observations on physical examination, a palpable mass was observed to occupy any portion of either breast (the left in 4 cases and the right in 2). These masses were well circumscribed, round, hard and freely movable and ranged in size "from that of a cherry to that of a fist." A few only were described as having a capsule.[11] The tumor appeared, as a rule, gray and, for the most part, solid. In 1 case a cyst was present,[11b] and in others [12] there were areas of calcification. The microscopic components consisted of hyaline cartilage and fibrocartilage, fibrous tissue and cartilage cells. The amounts of each varied in different cases. In some cases the fibrous tissue was rich in fibroblasts. Glandular elements were present in the tumor described by Davidsohn.

One would assume from the length of their duration that the tumors were benign. Yet in 1 instance a tumor present eighteen years recurred six months after excision. The author described nothing in the clinical history of the patient or in the pathologic condition of the tumor to indicate malignancy, unless one considers it significant that after fourteen years of quiescence the

10. Reports of cases by the following authors cited by Raso [19b] were not available to us: Monski, Salamoni, Guizzetti, DuBar, Molin, Soulier, DeSoil and Parreira.
11. (*a*) Amann, J. J.: Beitr. z. Geburtsh. u. Gynäk. **4**:57, 1860. (*b*) Pied: Bull. Soc. méd. de l'Yonne (1879) **20**:50, 1880. (*c*) Stefanini, D.: Gaz. d. osp. **9**:564, 1888. (*d*) Rey: Lyon méd. **100**:259, 1903.
12. Borst, M.: Geschwulstlehre **2**:881, 1902. Amann.[11a]

tumor renewed its growth and increased from "acorn to pullet egg size." Significantly, the recurrence was composed of hyaline cartilage, indicating its true neoplastic potentialities.

Facts worth noting are that no case of enchondroma of the human breast has been reported since 1909 and that there are no data on the ultimate outcome in the ones reported prior to that year. It would appear advisable, therefore, for future contributors to allow a sufficiently long period to elapse before publishing reports.

TABLE 1.—*Enchondroma*

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptoms	Treatment	Follow-Up
1. Amann: Beitr. z. Geburtsh. u. Gynäk. **4**: 57, 1860	1860	54	32 yr.	Growing mass; pain	Shelling out	None
2. Pied: Bull. Soc. méd. de l'Yonne (1879) **20**: 50, 1880	1879	14	1 yr.	Large left breast	Excision	None
3. Cambria: Riv. ven. di sc. med. **6**: 340, 1887	1887	19	18 yr.	Mass	Excision	Recurrence in 6 months
4. Stefanini: Gaz. d. osp. **9**: 564, 1888.....	1888	50	25 yr.	Mass; pain	Excision	None
5. Borst: Geschwulstlehre **2**: 881, 1902.....	1902	..	.....	No history	.....	.....
6. Rey: Lyon méd. **100**: 259, 1903.....	1903	25	6 yr.	Mass	Mastectomy	None
7. Davidsohn: Zentralbl. f. Gynäk. **33**: 1357, 1909	1909	51	?	Mass	Shelling out	None

TABLE 2.—*Chondrosarcoma*

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptoms	Treatment	Follow-Up
Coats: Glasgow M. J. **4**: 45, 1871.....	1871	..	No history	.....	.....	.....
Bowlby: Tr. Path. Soc. London **33**: 306, 1882..	1882	42	1 yr.	Mass	Mastectomy	Recurrence in 6 mo.; death; autopsy
Clarke: Tr. Path. Soc. London **41**: 229, 1891..	1890	46	2-3 yr.	Mass	Mastectomy	None
Poulsen: Arch. f. klin. Chir. **42**: 638, 1891.....	1891	..	.....	Mass	Excision	Recurrence 6 and 12 mo.; death 1 yr. later
Horner: Beitr. z. klin. Chir. **12**: 619, 1894.....	1894	59	49 yr.	Ulcerated mass; pain	Mastectomy	Well after 4 yr.
Happel: Beitr. z. klin. Chir. **14**: 721, 1895..... Wacker, cited by Happel	1895	33	10 yr.	Mass	Excision	None
Holder: Memphis M. J. **16**: 66, 1896.....	1896	12	9 mo.	Mass	Excision	None
Morton: Tr. Path. Soc. London **54**: 327, 1904..	1904	64	1 mo.	Mass	Mastectomy; axilla cleared	Several recurrences within 15 mo.; death shortly afterward
Guilbaud: Gaz. méd. de Nantes **24**: 372, 1906..	1906	?	13 yr.	Mass	Excision	None
Lecène: Rev. de chir., Paris **33**: 434, 1906.....	1906	25	?	Mass	Enucleation	None
Watson: Catalogue of the Museum of the Royal College of Surgeons, 1909	1909	60	2 mo.	Mass	?	Recurrence in 3 mo.
Orlando: Osp. maggiore **1**: 519, 1913.....	1913	..	No history	.....	.....	.....
Kaufmann: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 3, p. 1786	1922	57	27 yr.	Mass	?	.....
Thinnes: Virchows Arch. f. path. Anat. **264**: 150, 1927	1926	43	5-6 mo.	Mass	Mastectomy	None
D'Aunoy and Wright: Ann. Surg. **92**: 1059, 1930	1930	46	9 yr.	Mass	Mastectomy	None
Wakeley: Brit. J. Surg. **21**: 156, 1933.....	1933	89	?	Mass	Mastectomy	Well after 1 yr.
Berner: Ztschr. f. Krebsforsch. **46**: 232, 1937...	1937	53	?	Mass	Mastectomy	Recurrence in 9 mo.; died at 10 mo.; autopsy
Sailor (case 3): Am. J. Cancer **31**: 183, 1937...	1937	68	4 yr.	Mass	Biopsy	Died in 5 mo.
Anzilotti: Arch. ital. di med., Sperimentale **3**: 513, 1938	1938	56	1 mo.	Mass; pain	?	None
Allen: Arch. Path. **29**: 589 (May) 1940.....	1940	28	2½ yr.	Mass	Radical	.....

CHONDROSARCOMA

Twenty-one reports of malignant cartilaginous tumors of the breast were found, all occurring in females from 12 to 89 years of age. Most patients were aware of the growth for a long time, nine to forty-nine years. In addition to consciousness of a mass, 2 patients experienced pain.[13] In 1 of these this did not happen, until the tumor ulcerated through the skin and became infected. In those cases in which the tumor was present many years the rate of growth was usually slow at first and rapid later. In 1 instance it was continuously slow until the tumor achieved conspicuous size. In still another the growth enlarged only during periods of pregnancy. The most rapidly growing tumors were

13. (*a*) Horner, F.: Beitr. z. klin. Chir. **12**:619, 1894. (*b*) Anzilotti, G.: Arch. ital. di med., Sperimentale **3**: 513, 1938.

those discovered one to nine months before medical consultation.

In regard to physical observations, either breast was likely to be involved. The growths as a rule were freely movable. Only one became adherent to the skin, and this one ulcerated.

The patients were treated either by simple mastectomy or by excision. In 1 instance a radical operation [14] was done. Of the 6 patients for whom there were follow-up data, 2 were living one and four years after operation. The remaining 4 suffered recurrence in six to twelve months and were dead in one to two years. The prognosis is thus essentially poor.

The tumors varied from "pigeon egg, goose egg, apple size, to twenty centimeters" in diameter. In general they were irregular, round and sharply demarcated, and some were encapsulated.[15] Their color was given as gray-white and their consistency as dense, firm and hard.

In the case of Berner autopsy disclosed metastases to the chest wall, pleura and lungs, as well as recurrences in the skin about the operative scar. The pulmonary metastases were nodular and varied in size and distribution through the two lungs. Microscopic examination of the pulmonary tumors, of the mass in the wall of the chest and of the cutaneous recurrences showed a picture similar to that of the original tumor, namely, of cartilaginous composition and richness in giant cells. In Morton's case the gluteal metastasis was found to contain many round cells and cartilage undergoing calcification. In the breast the cells were of the spindle type.

OSTEOCHONDROMA

Eight cases of osteochondroma comprise this group. The essential available clinical data are summarized in table 3. Thereto the following supplemental facts should be added, namely that

TABLE 3.—*Osteochondroma*

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptoms	Treatment	Follow-Up
Durham: Brit. M. J. **2**:1019, 1883	1883	23	No history	No history	Excision	.....
Battle: Tr. Path. Soc. London **37**:473, 1886	1886	73	5 yr.	Mass	Mastectomy	No recurrence in 9 mo.
Leser: Beitr. z. path. Anat. u. Physiol. **11**:382, 1887	1888	67	16 yr.	Mass	Excision	None
Sehrt: Beitr. z. klin. Chir. **53**:589, 1907	1907	44	6 mo.	Mass	Mastectomy; axilla cleared	None
Chevrier and Delval: Bull. et mém. Soc. anat. de Paris **85**:586, 1910	1910	56	2 mo.	Mass	?	None
Fowler: Northwest Med. **24**:122, 1925	1925	67	10 mo.	Mass; pain	Radical	None
Dyke: Brit. J. Surg. **14**:323, 1926	1927	50	9 mo.	Mass	Mastectomy	None
Jäki: Deutsche Ztschr. f. Chir. **219**:413, 1929	1929	76	6 mo.	Mass	Excision	None

While some tumors presented a uniform appearance, others were in part hard and in part composed of solid soft tissue. Several were cystic. Three tumors contained areas of calcification.

All the tumors contained cartilage in varying amounts and variously distributed through a fibrous or cellular stroma. The cells were of diverse types, being spindle, round, oval or polymorphous. Three tumors [16] contained large multinuclear giant cells. Lecène described the cells in the case reported by him as of the "epulis" type. The stroma in a few cases appeared myxomatous.[17] In 3 cases remnants of glandular tubules were found in the tumor.

the tumors as a group were of slow growth, continuous in some cases and periodic in others; that only 1 patient suffered pain, and that the physical examination revealed a firm, freely movable, nontender mass, the overlying skin of which was smooth and uninvolved.

Grossly the tumors were hard and lobulated and varied from a few millimeters to 10 cm. in diameter. All were well demarcated, and four were encapsulated. While three specimens were cystic, five others were solid and composed largely of gray tissue in which, in some cases, bone and cartilage were grossly detectable.

Microscopically the tumors were composed of fibrous tissue, cartilage and spongy bone. In 1 case there was also osteoid tissue. Spindle, round and multinuclear giant cells constituted the cellular components of the tumors. The amounts of these elements varied from case to case. In 3 instances glands were found in the tumor. In Fowler's case calcification was shown.

14. Morton, C. A.: Tr. Path. Soc. London **54**:327, 1904.

15. Lecène, P.: Rev. de chir., Paris **33**:434, 1906. Anzilotti.[13b]

16. Berner, O.: Ztschr. f. Krebsforsch. **46**:232, 1937. Footnote 15.

17. (*a*) Poulsen, K.: Arch. f. klin. Chir. **42**:638, 1891, (*b*) Holder, A. B.: Memphis M. J. **16**:66, 1896. (*c*) Allen, A. C.: So-Callel Mixed Tumors of Mammary Gland of Dog and Man, with Special Reference to General Problem of Cartilage and Bone Formation, Arch. Path. **29**:589 (May) 1940. Anzilotti.[13b]

OSTEOCHONDROSARCOMA

In most of the cases in this group osteochondrosarcoma occurred in persons who were in the sixth decade and all of whom were older than 40 years. In contrast to the persons whose cases are summarized in the previous tables (who had growths for many years), the majority of those with growths of this type came under medical observation comparatively early. Their tumors varied in size and in rate of growth. In a case in which the neoplasm was neglected it attained the dimensions of a man's head, became fixed to the skin and ulcerated.

Arnold's patient noted a gradual enlargement of the breast. The surmise that there was an abscess led to the making of an incision. Since healing did not follow, the breast was removed. In Sailor's case growth was rapid; in the remaining cases no note was made of the rapidity of growth. In 3 cases the tumor proved definitely malignant; in 2 the patients remained well two to ten years after operation. No follow-up information was given in the remaining 5 cases.

The largest tumor measured 16 cm.; another, 8 by 10 cm.; the smallest was the size of a pigeon's egg. A few were freely movable and not fixed to surrounding structures. One tumor was described as sharply demarcated. Most were solid. Cysts were present in 3 cases.[18]

Microscopic examination revealed bone and cartilage in all the tumors. All were richly cellular, the cells being round, spindle and polymorphous in character. Large and multinucleated giant cells were noted in 7 cases. Bauer described as many as three hundred nuclei in the giant cells of his patient. The tumor in Kurosu's patient simulated an epulis growth. Two of the neoplasms were in part fibroadenoma.[19]

A word must be said concerning the nature of the recurrent tumors and the metastases in those cases in which autopsies were performed. The pulmonary metastases in Stilling's case contained osteoid tissue, cartilage and cellular elements. Two separate and distinct nodules were removed from Le Riche and Cavaillon's patient. One was carcinoma; the other, sarcoma containing cartilage and bone. At autopsy recurrent growths were found in the axilla and wall of the chest. These consisted of "complex cartilage." There were no generalized metastases. Busser first considered the tumor in his patient to be an adenofibroma exhibiting metaplasia of bone and cartilage. In the recurrence he noted cartilage, osteoid tissue, osteoblasts, numerous giant cells and areas of fibrosarcoma. The last was not seen in the original tumor. Removed from the thigh of Raso's patient was a metastatic growth containing bone and cartilage as well as cellular elements. Bone was not noted in the primary growth.

TABLE 4.—*Osteochondrosarcoma*

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptoms	Treatment	Follow-Up
Heurtaux: Bull. et mém. Soc. de chir. de Paris **1**:94, 1875	1874	52	6 mo.	Mass; pain	Mastectomy	Recurrence in 6 mo.; death; no autopsy
Stilling (case 2): Deutsche Ztschr. f. Chir. **15**: 247, 1881	1881	53	1½ yr.	Mass	Excision	Died following operation; metastasis to lung
Arnold: Virchows Arch. f. path. Anat. **148**: 449, 1897	1897	67	6 mo.	.....	Mastectomy; axilla cleared	None
Leriche and Cavaillon: Bull. et mém. Soc. anat. de Paris **83**: 400, 1908	1908	40	?	Mass	Mastectomy	Recurred; death in 2 mo.
Kaufmann: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929	1922	52	No history	No history	.....	.....
Kurosu: Ztschr. f. Krebsforsch. **26**: 99, 1927....	1927	80	6 mo.	Mass	Mastectomy	Death in 1 yr.; no information
Busser: Ann. d'anat. path. **5**: 340, 1928; **6**: 1247, 1929	1929	50	?	Mass	Mastectomy; axilla cleared	Recurrence in 1 yr.
Banet: Bull. Liga contra el cáncer **8**: 321, 1933	1933	57	2 yr.	Mass	Radical; roentgen	Well at 5 mo.
Sailor (case 4): Am. J. Cancer **31**: 183, 1937....	1937	50	6 wk.	Mass	Mastectomy	Well at 2 yr.
Raso: Pathologica **29**: 229, 1937.....	1937	45	2 mo.	Mass	Radical	10 mo. metastasis to lung; no autopsy
Sullivan: Illinois M. J. **82**: 140, 1942.....	1942	43	2 mo.	Mass	Excision	None
Freshman: Rocky Mountain M. J. **37**: 981, 1940	1942	52	3 yr.	Mass	Radical	Well at 10 yr.

OSTEOSARCOMA

As can be seen from table 5, "ossifying sarcoma" of the breast accounts for a small group of cases. In Schreiner's case the tumor was stationary for thirty-nine years, after which it

18. Arnold, S. K.: Virchows Arch. f. path. Anat. **148**:449, 1897. Sullivan, S. J.: Illinois M. J. **82**:140, 1942. Freshman, A. W., and Kurland, S.: Rocky Mountain M. J. **37**:981, 1940.

19. (*a*) Busser, F.: Ann. d'anat. path. **5**:340, 1928. (*b*) Raso, M.: Pathologica **29**:229, 1937.

grew rapidly. This patient died from intrathoracic metastasis one year after operation. The only clinical symptom in the entire group was a sense of mass.

Gross descriptions are meager. In general the tumors were globular, hard and cystic. All contained bone. In Sutton's case the microscopic picture was so similar to that of osteogenic sarcoma of bone that the patient was submitted to careful examination for a primary osseous tumor. Beckton noted the presence of considerable fibrous tissue and areas rich in cells, par-

TABLE 5.—*Osteosarcoma*

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptom	Treatment	Follow-Up
Stilling (case 1): Deutsche Ztschr. f. Chir. **15**: 247, 1881	1881	56	6 mo.	Mass	Excision	Died 2 years later; no autopsy
Sutton: Arch. Middlesex Hosp. **19**: 98, 1910...	1910	73	2 mo.	Mass	Mastectomy; axilla cleared	None
Beckton: Arch. Middlesex Hosp. **27**: 215, 1912	1912	52	5 mo.	Mass	Mastectomy; axilla cleared	None
Schreiner and Thibeaudeau: Ann. Surg. **95**: 433, 1932	1932	57	40 yr.	Mass	Excision; later mastectomy; postoperative roentgen therapy	Thoracic metastasis; died in 1 year; no autopsy
Gomori: Am. J. Surg. **33**: 150, 1936.....	1936	64	6 mo.	Mass	Mastectomy	None

TABLE 6.—*Osteoid Sarcoma; Giant Cell Sarcoma*

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptoms	Treatment	Follow-Up
Lancereaux: Bull. Soc. anat. de Paris **35**: 293, 1860	1860	46	8 mo.	Slow-growing tumor which ulcerated; lancinating pain	Excision	Follow-up period too short
Haward: Tr. Clin. Soc. London **7**: 106, 1874....	1874	64	13 yr.	Recurring tumor	Excision; then mastectomy	Involvement of chest wall; death; autopsy
Stilling (case 3): Deutsche Ztschr. f. Chir. **15**: 247, 1881	1881	59	10 yr.	Mass; pain	Mastectomy	Nine recurrences; death; autopsy
Pillier: Bull. et mém. Soc. anat. de Paris **4**: 552, 1890	1890	No history				
Noetzel: Ein Beitrag zur Kenntnis der Fibroadenome der weiblichen Brustdrüse, Berlin, G. Schade, 1892	1891	No history				
Snow: Tr. Path. Soc. London **46**: 184, 1895...	1895	62	.....	No further history		
Manz: Beitr. z. klin. Chir. **13**: 66, 1895.....	1895	52	3 mo.	Rapidly growing mass	Radical	Recurrence
Heuter and Karrenstein: Virchows Arch. f. path. Anat. **183**: 495, 1906	1906	37	12 yr.	Mass, stationary for 11 years	Mastectomy	Recurrence in 5 mo.; death in 1 year with metastasis to lung
Lorrain and Ménard: Bull. et mém. Soc. anat. de Paris **84**: 103, 1909	1909	86 Male	1 yr.	Rapidly growing mas	None	Death shortly after admission to hospital
Desmarest and Masson: Bull. et mém. Soc. anat. de Paris **87**: 281, 1912	1912	52	12 yr.	Mass	Radical	No follow-up
Orlando: Osp. maggiore **1**: 519, 1913.....	1913	No history				
Moure and de Jong: Bull. et mém. Soc. anat. de Paris **89**: 32, 1914	1914	67	2 yr.	Mass	Mastectomy	Death in 2 mo.
Jessup: Proc. New York Path. Soc. **19**: 117, 1919	1919	..	6 mo.	Mass	Mastectomy	Axillary nodes involved
Fry: J. Path. & Bact. **30**: 528, 1927.....	1927	55	5 mo.	Mass	Radical	Death in 10 mo., probably from metastasis to lung; no autopsy
Edelmann: Beitr. z. path. Anat. u. z. allg. Path. **78**: 618, 1927	1927	51	.....	Mass	Excision	None
Wellbrock: Ann. Surg. **90**: 154, 1929.....	1929	57	2 mo.	Mass	Mastectomy	Recurrence in 3 mo.
Caligaris: Cancro **3**: 226, 1933.....	1932	64	6 mo.	Mass	Radical	Death in 2 mo.; diagnosis, pneumonia; no autopsy
Hartmann and others (case 1): Bull. Assoc. franç. p. l'étude du cancer **22**: 378, 1933	1933	27	19 yr.	Mass	Excision; radical	Death in 2½ years, apparently from metastasis
Hartmann and others (case 2): Bull. Assoc. franç. p. l'étude du cancer **22**: 378, 1933	....	60	30 yr.	Mass	Excised	Recurrence in 4 mo.; death in 9 mo.; metastasis to lung
Hartmann and others (case 3): Bull. Assoc. franç. p. l'étude du cancer **22**: 378, 1933	....	..	3 wk	Mass	Excision; radium	Prompt recurrence; 1 year later evidence of bony metastasis
Rose: Deutsche Ztschr. f. Chir. **246**: 151, 1936	1935	36	10 yr.	Mass	.....	Death in 6 mo.; no autopsy
Guérin: Bull. Assoc. franç. p. l'étude du cancer **25**: 326, 1936	1936	68	1 mo.	Mass	Radical; cartilage also present	Pulmonary metastases; death in 17 mo.
Di Stefano: Tumori **23**: 482, 1937.....	1937	50	.....	Mass	.....	.....
Holm (case 1): Acta path. et microbiol. Scandinav. **17**: 506, 1940	1940	50	20 yr.	Mass	Excised	Recurrence; mastectomy; death from pulmonary embolism
Holm (case 2): Acta path. et microbiol. Scandinav. **17**: 506, 1940	....	62	2 mo.	Mass	Mastectomy	Death in 6 weeks

ticularly giant cells having as many as sixty nuclei. The histologic picture in Schreiner's case was essentially similar, except that some of the connective tissue had undergone myxomatous change.

OSTEOID SARCOMA; GIANT CELL SARCOMA

A variety of descriptive names have been coined for the tumor now to be discussed. It is one rich in polymorphous cellular elements, the most characteristic of which is a large giant cell having as many as twenty-five to sixty nuclei. These cells have been likened by some writers to those of the epulis tumor; by others, to osteoclasts. By the French they have been called *myéloplaxes* and by the early English writers "myeloid cells." In addition to cells, these tumors may have a dense fibrous stroma and, in the most typical cases, osteoid tissue containing cells resembling osteoblasts. Decision as to cases belonging in this group proved difficult because many appearing for other reasons to do so lacked descriptions of osteoid tissue. This of course may have been due to the fact that such tissue was absent. However, a recent experience of one of us (A. R.) demonstrated that osteoid can be easily overlooked, for in a case being studied it was not found until many sections from diverse parts of the tumor had been prepared. This led us to the belief that absence of a description of osteoid was not sufficient grounds for excluding a tumor from membership in this group, and our table is compiled accordingly. Hartmann and his co-workers apparently had the same thought, for, despite the fact that 1 of their patients had osteoid and 2 did not, they nevertheless considered the cases of all 3 as identical. Thus grouped, there were 25 cases, 10 with osteoid tissue. In the remainder it was either absent or, if present, unobserved or not described.

The age distribution of the patients can be gathered from table 6. Of interest is the fact that in many instances the tumor had been present for many years (thirty in 1 instance). In general tumors of long standing grew slowly, either progressively or periodically. Some grew rapidly in the latter part of their course, while others, especially those recently described, grew rapidly from the time they were first noticed. The principal symptom was a sense of mass. Several tumors became adherent to the skin and ulcerated. In a few instances the growth softened and fluctuated. It was not unusual for the skin overlying the tumor to become violaceous and for the veins to become prominent. The modes of treatment varied from simple excision to radical surgical procedures. None seemed to affect the ultimate course, for in cases in which data were available they showed the outcome to be invariably fatal. Recurrence occurred within five months and death within twelve to fourteen months or earlier.

Grossly the tumors were characteristically circumscribed and in some cases encapsulated. Cysts filled with disintegrated hemorrhagic material were observed in many cases. The preserved solid portions were usually gray, reddish gray and soft. Their size varied from that of a small walnut to as large as 30 by 28 by 18 cm., and they weighed up to 4,500 Gm.

The histologic features have already been mentioned.

In cases of neglected tumor the growth infiltrated the thoracic cage. In cases in which treatment was given the tumors frequently recurred in the scar. The lungs were the usual site of metastasis. In 1 case metastases were found in the heart.[20] In cases in which it was possible to study the metastases and recurrences, the tumor reproduced the parent growth grossly and microscopically. The same cystic changes were seen. Also present were the characteristic giant cells and spindle cells, and, finally, even osteoid was reproduced.

MIXED TUMOR

Mixed tumor has been infrequently reported. The majority of the reports appearing in the literature have been contributed by French investigators, and it was they who gave them the name of *tumeurs mixtes*. The tumors may involve either breast, are circumscribed and freely movable and have attained sizes up to that of a fist. Only one[21] seems to have grown rapidly from the time it was discovered and to have recurred after removal. The chief characteristic of the tumor is the presence of cysts lined with stratified squamous epithelium. Some cysts contained keratin. In 1 case hair follicles were present.[22] In another there was, in addition, tissue resembling giant cell sarcoma.[21] Two contained cartilage[23] and 1 osteoid tissue.[23b] One tumor appeared to be fibroadenoma[23b] in which epidermoid cysts were also observed.

20. Stilling, H.: Deutsche Ztschr. f. Chir. **15**:247, 1881.

21. Nadal, P.: Bull. et mém. Soc. anat. de Paris **85**:616, 1910.

22. Gioia, T., and Bianchi, A.: Semana méd. **2**:1193, 1930.

23. (*a*) D'Allaines, F., and Hiely, J.: Ann. d'anat. path. **5**:361, 1928. (*b*) Duboucher, H.; Montpellier, J., and Laffargue, P.: Algerie méd. **30**:570, 1934.

TERATOMA AND CHONDROLIPOMA

Two tumors of particularly rare occurrence are teratoma and chondrolipoma, only 1 of each being reported. In 1923 McIver [24] described in a 60 year old woman a tumor, which in three months grew from the size of a walnut to that of an orange. After removal it proved to be spheroidal, and in it was an alveolar process with teeth. On microscopic examination, osteoid, cartilage and connective tissue were also found.

In 1906 Sick [25] noted in a 72 year old woman a mass composed of cartilage and fat which he diagnosed as chondrolipoma. Grossly the tumor was found to be encapsulated and to resemble a fibroadenoma.

TABLE 7.—*Mixed Tumor*

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptoms	Treatment	Follow-Up
Lecène: Bull. et mém. Soc. anat. de Paris **79**: 698, 1904	1904	54	2 mo.	Mass	Mastectomy; axilla cleared	None
Nadal: Bull. et mém. Soc. anat. de Paris **85**: 616, 1910	1910	44	2 mo.	Mass	Mastectomy	Recurrence in 7 mo.
D'Allaines (case 1) and Hiely (case 2): Ann. d'anat. path. **5**: 361, 1928	1928 1928	19 No history	1 yr.	Mass	Excision	None
Gioia and Bianchi; Semana méd. **2**: 1193, 1930	1930	45 (man)		.....	.....	None
Duboucher and others: Algérie méd. **30**: 570, 1934	1934	19	Many months	Mass	Excision	None

TABLE 8.—*Ossifying-Chondrifying and Giant Cell Tumor Associated with Carcinoma*

Author	Year	Age	Onset	Symptoms	Treatment		Follow-Up
Wagner: Arch. d. Heilk. **2**: 275, 1861	1861	53	2 yr.	Mass	Excision	Enchondroma and carcinoma	Well at 4 mo.
Lange: M. Rec. **20**: 161, 1881.....	1881	51	20 yr.	Mass	Mastectomy; axilla cleared	Osteochondroma and carcinoma	None
Gross: Am. J. M. Sc. **94**: 494, 1887....	1887	74	6 mo.	Mass	Mastectomy	Osteoma and carcinoma	None
Coen: Boll. d. sc. med. di Bologna **2**: 302, 1891	1891	51	9 yr,	Mass	Excision	Osteochondroma and carcinoma	None
Takano: Arch. f. klin. Chir. **103**: 155, 1913-1914	1914	49	3 mo.	Mass	Radical	Carcinoma; chondrosarcoma	None
Kreibig: Virchows Arch. f. path. Anat. **256**: 42, 1925	1925	50	Several months	Mass	Mastectomy	Osteosarcoma and carcinoma	None
Biehl: Beitr. z. klin. Chir. **140**: 59, 1929	1927	55	8 mo.	Mass	Radical	Osteoid sarcoma and carcinoma	None
Budd and Breslin: Am. J. Cancer **31**: 207, 1937	1937	59	29 yr.	Mass	Excised	Carcino-osteogenic sarcoma	4 yr. post operation, well; free of recurrence or metastases
Tudhope: J. Path. & Bact. **48**: 499, 1939	1939	63	3 yr.	Mass; pain	Radical	Osteoid chondrosarcoma and carcinoma	None

OSSIFYING-CHONDRIFYING AND GIANT CELL TUMOR ASSOCIATED WITH CARCINOMA

The cases in this group, like those in the others, represent a rare form of neoplasm. Wagner entitled his report, "A Case of Enchondroma and Carcinoma of the Breast." The tumor was the size of a goose egg, circumscribed and composed of fibrous tissue, fusiform cells and cartilage. His description of the carcinomatous elements was not clear. Von Hacker,[26] who conducted the pathologic study of Lange's tumor, concluded that the specimen was a mixed tumor containing cartilage and bone which doubtless originated in a cystadenoma of the breast and parts of which later changed to carcinoma. Gross described a circumscribed tumor composed of bone in which elements of carcinoma were present. He felt that the primary growth had originally been a fibroadenoma. The tumor in Coen's case was largely bone, with some cartilage and epithelial elements—the latter giving it a resemblance to alveolar carcinoma. Takano described a tumor composed of two elements, carcinoma and sarcoma. Also present were foci of cartilage. The lymph nodes in this case contained adenocarcinoma. Kreibig summarized his case thus: "For the most part the tumor is osteosarcoma in which there are also present fibroma, cavernoma, and two lobules of carcinoma." From Biehl's report we quote:

24. McIver, M. A.: Ann. Surg. **77**:354, 1923.

25. Sick, C.: Jahrb. d. Hamb. Staatskrankenanst. (1906) **11**:17, 1907.

26. von Hacker, V. R.: Arch. f. klin. Chir. **27**:614, 1882.

"The tumor contained numerous giant cells, polymorphous elements, cartilage, osteoid and carcinoma." Budd and Breslin reported on a tumor part of which was osteogenic sarcoma and part carcinoma. In places these elements were intimately intermixed. Typical epulis-like cells were present.

CARCINOSARCOMA

It is our intention, not to review the literature on carcinosarcoma, but only to note that in some of the reports it is stated that the sarcomatous portion of the growth contained epulis-like cells in large numbers as well as spindle and polymorphous cells, so that there was a strong resemblance to osteoid giant cell tumor. In this group fall the cases of Billroth,[27] Fox,[28] Helwig,[29] Schlagenhaufer [30] and possibly that of Wilensky.[31]

COMMENT

A group of cases of osteogenic and chondrogenic tumors arising in the breast have been studied. As can be seen from the relatively few reports which have appeared in the literature since 1700, their occurrence in human beings has been uncommon. In contrast, such tumors were found more frequently in breasts of lower mammalia (dogs, goats, cows). In 1860 Virchow [32] stated that chondroma was unusually frequent in dogs. In 1910 Glendining [33] likewise reported fibrochondroma, ossifying chondroma and chondrifying fibrosarcoma in dogs. More recently Allen [17c] corroborated Virchow and Glendining, reviewed the literature, and added 4 more cases of canine tumor and 1 of a similar tumor occurring in a human female.

When individual cases of chondroma, osteogenic sarcoma, giant cell tumor and the others are compared one with the other, no interrelationship may be seen. However, when all the cases are studied and viewed as a whole, basic similarities become apparent. Then such differences as do exist appear to be due to varying degree of development of the different tumor elements or to the fact that some one element has developed either not at all or so slightly as to escape notice. This is well illustrated by a study of individual reports. Thus Guérin presented his case as an instance of typical osteoid sarcoma, which in truth it appears to be, except that a small amount of cartilage was present. The growth observed by Morton was described by him as composed of cartilage and a moderate number of spindle cells and large, multinucleated giant cells. Only after a committee restudied his case was osteoid tissue noted. In Raso's patient the primary tumor contained cartilage. In the metastasis there was, in addition, cartilage undergoing ossification. Thus a tumor which at first seems to belong in a certain category is later grouped in another because of added observations. Certain threads of similarity relate these seemingly different tumors to each other. In almost all, for instance, the same cellular components are found—spindle, polymorphous and large multinuclear giant cells. Furthermore, in many cases the parent tumor appears to have been a fibroadenoma. So, to us at least, it seemed that a particular tumor could properly be classified as belonging to several groups. For this reason it is our opinion that, however a given case may be classified, it is sound judgment to regard all these cases as related.

References to the fact that portions of tumors presented the picture of fibroadenoma were found in the earliest writings. Later observers swelled the literature with new cases. The following is a tabulation of the types of tumor with the number of cases of each type in which fibroadenoma was detected:

Types	Number of Cases
Chondroma	1
Osteochondroma	1
Osteochondrosarcoma	2
Chondrosarcoma	1
Mixed tumor	3
Giant cell tumor	10

Some of the fibroadenomas were intracanalicular and others pericanalicular. In his case 3, Stilling noted a small circumscribed fibroadenoma adjacent to the giant cell tumor. From this he postulated that the former probably arose in a fibroadenoma. In the breast described by Desmarest and his associates, five circumscribed masses were found, four fibroadenoma and the fifth a giant cell tumor. In case 3 of Hartmann and associates a giant cell tumor appeared eight years after a fibroadenoma was removed from the breast. Review of the slides from the first

27. Billroth, T., and Luecke, A.: Handbuch der Frauenkrankheiten, Stuttgart, F. Enke, 1886, vol. 3, p. 58.

28. Fox, S. L.: Ann. Surg. **100**:401, 1934.

29. Helwig, F. C.: Carcinoma of Breast Combined with Giant Cell Sarcoma, Arch. Path. **4**:162 (Aug.) 1927.

30. Schlagenhaufer: Zentralbl. f. allg. Path. u. path. Anat. **17**:385, 1906.

31. Wilensky, A. O.: Proc. New York Path. Soc. **19**:113, 1919.

32. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863, vol. 1, p. 134.

33. Glendining, B.: Arch. Middlesex Hosp. **19**:198, 1910.

growth revealed, after careful study, the presence of large multinucleated giant cells. In Pillier's case two tumors were present. One was a fibroadenoma and the other a giant cell tumor. The presence of these fibroadenomas led many authors to conclude that in their case at least the parent growth was the fibroadenoma and that from its tissues cartilage, osteoid, bone and carcinoma had developed.

Following this train of thought, one begins to wonder whether, in those instances in which tumors were observed for long periods, fibroadenoma did not precede the stage of mixed tumor. The mere fact that fibroadenoma was not described does not mean that it was absent in these cases. This was impressed on us by a case which we studied in which intracanalicular fibroadenoma was demonstrated only after the entire tumor was subjected to sectioning.

A word should be said on the life cycle of these tumors as a group. In most cases they were present many years, growing slowly and progressively. Others remained stationary for long periods, after which they proceeded to grow again at a rapid rate. Though most of the tumors remained circumscribed, freely movable and nonadherent, a few eventually ulcerated through the skin and fungated outward. When neglected, they infiltrated through the chest wall into the thoracic cage. No matter what form of surgical treatment was employed—excision, mastectomy or radical—in many cases metastasis followed. Degenerative phenomena in the tumor were not uncommon, these consisting of cystic change, calcification, myxomatous degeneration and necrosis.

Since follow-up studies were lacking in many instances, the complete number with recurrence, metastasis and fatal outcome cannot be given. Of the total group of enchondromas there were data concerning recurrence in 1 case only. This occurred six months after operation. The recurrence reproduced cartilage, as had the parent tumor. Of the chondrosarcomas five recurred in six to nine months, and all the patients were dead in ten to twenty-four months after surgical treatment. Two recurrences were studied histologically and were found to be similar to the parent growth. Both also showed distant metastases to lung, skin and gluteal muscles. There were no data on the osteochondromas. Osteochondrosarcoma proved to be extremely malignant, 6 patients having recurrences in six to ten months and 5 dying one year after first observation. The recurrent and metastatic tumor reproduced bone and cartilage in addition to the pleomorphic cellular elements present in the parent tumor. Of the growths labeled "mixed tumor" one recurred in seven months. Two of the patients with osteosarcoma died of their tumors one and two years respectively after operation. The giant cell tumors proved to be particularly vicious; fourteen recurred in a few months and caused death in seventeen months. In Stilling's case which came to autopsy there was disclosed a metastasis to the heart. This was a typical giant cell tumor with osteoid tissue. In the case of Moure and De Jong metastasis was demonstrated in the lung. In many of the remaining cases there also appeared to be pulmonary metastases, but, unfortunately, there were no autopsies to prove it. In the case of Jessup, lymph nodes were involved by tumor. The only other type with metastasis to lymph nodes was that associated with carcinoma.

There is considerable discussion in the literature regarding the histogenesis of these tumors. Very early some authors discussed the possible presence in a dormant state of skeletal tissue extruded from rib or clavicle and considered whether such inclusions might at a later date serve as the seed for tumor. This hypothesis has not progressed beyond the phase of theoretic possibility.

Another group has advanced for consideration the possibility of a teratomatous origin. Again, proof of this has not been forthcoming. In all the literature reviewed we could find only 1 example of teratoma of the breast.

The most widely supported view is that ascribing to the tumors a metaplastic origin. It has been demonstrated with reasonable conclusiveness that osteoid and bone may arise in hyalinized collagenous elements.[34] The demonstration of chondroid anlage is less clear. In his study on canine tumor, Allen has offered proof of its origin in adult epithelium as well as in mesenchymal cells.

There are differences of opinion as to the nature of the cellular elements of these tumors. Most investigators have taken it for granted that the spindle and polymorphous cells are true sarcoma cells; others are convinced that the giant cells are osteoclasts and that the polyhedral cells within and about the bone are osteoblasts. After study of the material from the cases of Jessup and of Budd and Breslin,[35] Ewing [36] expressed his view that the cellular components were car-

34. Binkley, J. S., and Stewart, F. W.: Morphogenesis of Extraskeletal Osteogenic Sarcoma and Pseudo-Osteosarcoma, Arch. Path. **29**:42 (Jan.) 1940.

35. Budd, I. W., and Breslin, F. J.: Am. J. Cancer **31**:207, 1937.

36. Personal correspondence with Budd and Breslin.[35]

cinoma. At a later date Stewart, restudying slides from the case of Budd and Breslin, came to the same conclusion. Mallory and Masson,[36] who also studied material from this case, felt that the tumor was sarcoma. One fact brought to the foreground by our review which may lend support to their belief is the total absence of metastasis to lymph nodes, that in Jessup's case being the sole exception.

CONCLUSION

Tumors characterized by bone formation, cartilage, fibrous tissue and pleomorphic cells—thus strongly simulating osteogenic and chrondrogenic tumors—occur in the breast.

These tumors are essentially malignant.

Long-standing fibroadenoma is in many cases the parent growth from which they arise.

The osteoid and bone elements probably arise by metaplasia from hyalinized collagen. The mode of origin of cartilage is less clear.

The nature of the cellular component has evoked divergent opinions, some authors saying that it is carcinomatous and others that it is sarcomatous.

METABOLIC ALTERATIONS FOLLOWING THERMAL BURNS

III. EFFECT OF VARIATIONS IN FOOD INTAKE ON NITROGEN BALANCE OF BURNED PATIENTS

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DETROIT

In 1926 Davidson [1] demonstrated that severely burned patients excrete abnormally large amounts of nitrogen in the urine, a finding which has been confirmed by other investigators.[2] Although the existence of this abnormality of protein metabolism in burned patients has been well established, its mechanism is not understood, nor is there much information regarding the means of preventing or compensating for this destruction of body protein. The present study was undertaken to obtain more information about the change in protein metabolism in burned patients. It was planned to correlate the nitrogen balance of patients on various diets with the urinary excretion of 17-keto steroids, cortin-like substances, gonadotropins and estrogens. The purpose of this paper is to present studies on the nitrogen balance of 23 patients; the data on the endocrine changes in these patients will be presented elsewhere.

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1. Davidson, E. C.: Sodium Chloride Metabolism in Cutaneous Burns and Its Possible Significance for a Rational Therapy, Arch. Surg. **13**:262-277 (Aug.) 1926.

2. (*a*) Lucido, J.: Metabolic and Blood Chemical Changes in a Severe Burn: A Case Report, Ann. Surg. **111**:640-644, 1940. (*b*) Taylor, F. H. L.; Levenson, S. M.; Davidson, C. S.; Adams, M. A., and MacDonald, H.: Abnormal Nitrogen Metabolism in Burns, Science **97**:423, 1943. (*c*) Taylor, F. H. L.; Levenson, S. M.; Davidson, C. S., and Browder, N. C.: Problems of Protein Nutrition in Burned Patients, Ann. Surg. **118**:215-224, 1943.

MATERIALS AND METHODS

A ward of four beds with an adjoining workroom was established, and the patients were under the care of nurses trained in the methods of collection. Although in general the periods of metabolic study were five days, in a few instances shorter or longer periods were employed for some special reason. Metabolic studies were usually instituted within a few hours of the injury, but since some of the patients were intoxicated and uncooperative on admission to the hospital, it was occasionally necessary to postpone the first metabolic period. The first few patients were given a diet considered adequate for the maintenance of weight and nitrogen equilibrium during minimal activity. The diet was planned so that approximately 20 per cent of the calories was derived from protein, 20 per cent from fat and 60 per cent from carbohydrate. Subsequent patients received a diet of the same composition but in larger amounts. The amount of food consumed was determined by weighing the uneaten portion. A duplicate of the diet actually eaten by the patient was weighed and saved for nitrogen analysis. Liquid food was measured in graduated cylinders, and aliquots were removed for analysis.

The diet was planned to give the patients an equal quantity of nitrogen each day. Inasmuch as ordinary food varies considerably in nitrogen content, a synthetic diet of uniform composition was given by tube whenever possible. Generally administration of the diet started during the acute phase of the burn, when it is difficult to persuade patients to eat, and was continued as long as the tube was tolerated. The synthetic diet was composed of Nutramigen,[3] Amigen,[3] Dextri-Maltose [3] and vitamins,[4] in varying proportions. With subsequent patients a diet of eggnog and orange juice was employed instead of the synthetic diet.

The synthetic and eggnog diets were supplemented with ascorbic acid, 200 mg.; nicotinic acid, 40 mg.; thiamine hydrochloride, 4.5 mg.; riboflavin, 2 mg., and percomorph liver oil, 5 drops. The diet of conventional food was supplemented with ascorbic acid, 100 mg.; thiamine hydrochloride, 4.5 mg.; riboflavin, 6 mg.;

3. Supplied by Mead Johnson and Company, through the courtesy of Dr. Warren M. Cox Jr., and Mr. R. J. McElroy. "Nutramigen is a food composed of Dextri-Maltose (maltose and dextrins), Amigen, olive oil, arrowroot starch, calcium gluconate, brewers' yeast powder and minerals. Amigen is a dried enzymic digest of purified casein and pork pancreas containing amino acids and polypeptides." (Mead Johnson and Company).

4. Supplied by Merck & Co., Inc., through the courtesy of Dr. D. F. Robertson, and by Mead Johnson and Company, through the courtesy of Dr. Warren M. Cox Jr. and Mr. R. J. McElroy.

nicotinic acid, 30 mg., and 4 drops of blended oil containing vitamins A and D, with a potency of 4,250 U.S.P. units of vitamin A and 425 U.S.P. units of vitamin D per gram. One patient (D. H.) received 400 mg. of ascorbic acid, 10 mg. of thiamine hydrochloride, 10 mg. of riboflavin, 60 mg. of nicotinic acid, 100 mg. of pyridoxine, 100 mg. of calcium pantothenate and 8 drops of percomorph liver oil for the first ten days, and 100 mg. of ascorbic acid, 2 mg. of thiamine hydrochloride, 3 mg. of riboflavine, 20 mg. of nicotinic acid, 25 mg. of pyridoxine, 25 mg. of calcium pantothenate, and 3 drops of percomorph liver oil for the remainder of her stay in the hospital.

All nitrogen-containing material given intravenously, such as plasma, whole blood and casein hydrolysate,[5] was measured, and an aliquot was saved for nitrogen analysis. The figures for the oral and the parenteral intake of nitrogen therefore represent values obtained by actual analysis of the food and of parenteral fluids. The caloric intake was calculated from standard food tables.

The patients voided or were catheterized at the beginning of the first metabolic period and at the end of each subsequent period. Retention catheters were employed for the patients with burns of the perineum and for those who were too ill to cooperate in securing all samples of urine. The urine voided during each twenty-four hours was pooled in a large bottle and stored in the ice box. At the end of each twenty-four hours the volume was measured and an aliquot removed for chemical analysis. The aliquots were stored in the ice box under toluene, and, except when daily determinations were made, the aliquots for five days were pooled. The remainder of the urine was saved for hormone assays.

The exudate from the burned area was collected and analyzed according to a method previously described.[6] Dressings were applied at the beginning of each metabolic period and with a few exceptions were changed at the conclusion of the period. It was not feasible to collect the exudate from every patient. Carmine was employed to mark the feces, which were pooled for each period and analyzed for nitrogen. If the patient vomited, the vomitus was collected and the nitrogen content determined. The methods of preparation and analysis of the metabolic specimens have been previously described in detail.[7]

Lack of knowledge regarding the utilization of nitrogen administered in the form of transfusions of blood or plasma [8] makes it difficult to know how it should be considered in estimating the nitrogen balance. For this reason, in determining the balance, nitrogen given intravenously as blood or plasma was arbitrarily omitted. However, the amount of nitrogen derived from this source is presented in column 10 of the table.

RESULTS

Only rarely do burned patients have a desire for more than minimum quantities of food. Our patients were able to consume a diet slightly above their basal caloric requirement, but frequently when larger quantities of food were given, nausea, vomiting, diarrhea and mental confusion resulted. These symptoms were usually encountered in the first week. They occurred regardless of the type of food but were most pronounced in patients receiving the synthetic diet by tube. Whether the symptoms were produced by excessive amounts of amino acids, calories or water is not known. Sometimes these patients vomited enough to lower materially their caloric and nitrogen intake (G. R., section C of table), a circumstance that necessitated revision of their diet. For these reasons the protein, carbohydrate and caloric intake of the patients, especially those who had forced feeding, was not as constant as desired.

Of the patients whose burns exceeded 30 per cent of their body surface, only 2 (C. W. and M. Mc.) lived ten days or longer. One patient (F. H.) with 64 per cent of her body burned, lived for seven and one-half days. The other patients (D. B. and E. B.) with 30 per cent or more of the body surface burned did not survive long enough to permit any conclusions to be drawn from a study of their nitrogen balance.

All the patients excreted abnormally large quantities of nitrogen in the urine. The results of the urinary nitrogen partition will be reported in a subsequent publication. They are not in agreement, however, with the results of Taylor and associates,[2b] who found in some of their patients "large increases in the residual nitrogen of the urine, both in the absolute amount and in the percentage of the total nitrogen excreted."

Except for a few patients who received abnormally large quantities of protein and carbohydrate, all the patients were in negative nitrogen balance. The negative balance was usually most pronounced during the first ten days and gradually decreased thereafter (table). The patients who were in pronounced negative nitrogen balance lost weight, and some became visibly emaciated. As one would expect, the nitrogen deficit did not reflect the changes in weight. For example, R. Mc. lost approximately 19.4 Kg. in eighteen days, while the nitrogen lost, which did not include that lost from the wound, was only 194.5 Gm., or, in terms of muscle,[9] about 6 Kg.

It does not appear that there is a direct correlation between the extent or depth of the burn and the loss of nitrogen in the urine. This lack of correlation was probably due to many variables such as the type of bacteria that infects the burned area, the state of the patient's nutrition before the burn, the degree of muscular develop-

5. Supplied by Frederick Stearns & Company, Detroit.

6. Hirshfeld, J. W.; Williams, H. H.; Abbott, W. E.; Heller, C. G., and Pilling, M. A.: Significance of the Nitrogen Loss in the Exudate from Surface Burns, Surgery **15**:766-773, 1944.

7. Macy, I. G.: Nutrition and Chemical Growth in Childhood, Springfield, Ill., Charles C Thomas, Publisher, 1942, vol. 1.

8. Elman, R.: Maintenance of Nitrogen Balance by the Intravenous Administration of Plasma Proteins and Protein Hydrolysates, Physiol. Rev. **24**:372-389, 1944.

9. Muscle is assumed to be 20 per cent protein, and the factor for converting nitrogen to protein is 6.25.

Patient; Sex; Age	Per Cent of Body Burned: Total	3d Degree	Location	Days After Burn	Weight in Kg.	Average Temperature per Period, F.	Estimated Basal Caloric Requirement *	Caloric Intake per Day †	Calories per Kg. per Day ‡	Nitrogen Intake, Gm. per Day: Oral	Parenteral
					A						
J. C. M 46 yr.	9	5	Hands and forearms	1-5	....	99.2	.....	2,305 F	....	9.9	.....
				6-10		98.4		2,274 F		11.8	
				11-15		98.4		2,078 F		11.5	
				16-20		98.4		1,788 F		10.8	
				21-24		98.4		1,788 F		10.9	
B. P. M 40 yr.	10	4	Face, neck, arms and back	2-6	....	100.8	1,267.2	1,785 F	36.6	9.1	2.4 (plasma)
				7-11		100.5		1,755 F		9.6	
				12-15		99.0		1,854 F		9.9	
				16-20	48.8	98.9		1,855 F		9.6	
				(admission 62.4)							
R. H. M 16 yr.	10	0	Hands and forearms	1-5	56.8	99.6	1,629.6	1,704 S	27.3	9.8	.....
				6-10	55.4	98.9		1,704 S		9.4	
				(admission 73.2)							
R. Mc. M 43 yr.	22	22	Legs, thighs, buttocks, genitalia and perineum	5-9	....	100.4	1,514.4	2,180 F	29.8	8.8	.....
				10-13		99.1		2,028 F		11.0	
				14-18		100.9		2,028 F		11.3	
				19-23	53.8	100.6		2,734 F	37.3	14.1	5.3 (amino acids)
H. S. M 43 yr.	21	0	Face, neck, arms and hands	1-5	80	100.2	1,612.8	2,144 S	26.8	14.9	1.6 (plasma)
				9-13		100.4		2,505 S & F	31.3	14.8	
				14-18		100.6		2,528 F		13.9	
				19-23		99.7		2,528 F		13.5	
				24-27		98.2		2,559 F		16.4	
				28-32		98.2		2,617 F		15.8	
				33-37	69.5	98.3		2,509 F		17.2	
C. W. M 42 yr.	33	25	Face, neck, arms, shoulders and back	1-5	....	101.4	.....	1,675 F	....	8.4	6.8 (plasma)
				6-10		102.3		1,892 F		10.8	
E. L. F 38 yr.	8	8	Breast, arm and shoulder	32-36	....	98.8	.....	1,304 F	....	7.4	.....
				37-41		98.7		1,497 F		8.8	20.0 (blood)
				42-47		99.9		1,358 F		5.7	
I. V. F 22 yr.	16	1	Arms, forearms, scalp and neck	1-5	77.3	99.3	1,560.0	2,022 S	26.2	12.5	.....
				6-10		98.9		2,550 F	32.9	20.5	
				11-15	78.8	98.9		2,550 F		21.6	
M. Mc. F 30 yr.	32	2	Abdomen, chest, back, buttocks, thighs and external genitalia	1-5	....	100.9	.....	1,338 F	....	7.8	4.1 (plasma)
				6-10		101.6		1,342 F		8.0	
				11-15		101.2		1,278 F		7.9	
				16-20		101.1		1,348 F		7.8	
				21-25		99.8		1,344 F		8.0	
				26-30		99.4		1,276 F		7.2	
E. B. F 41 yr.	84	Most of body	.....	1	59.1	100.4	1,255.2	2,134 S	36.1	17.7	49.1 (plasma)
					B						
A. M. M 51 yr.	6.5	0	Hands and forearms	1-5	60.0	99.4	1,360.8	4,389 S	73.2	25.4	1.4 (plasma)
				6-10	63.4	98.5		4,528 S	75.5	26.3	
				11-15		97.7		2,935 F	48.9	20.3	
				16-20	62.8	97.9		2,935 F		20.5	
				21-25		97.8		2,935 F		19.8	
				26-30	63.9	97.8		2,974 F		23.4	
				33-38	63.0	97.9		2,869 F		21.0	
I. G. M 25 yr.	12	2	Hands, face, neck, legs, thighs and shoulders	1-2	85.4	101.0	1,764.0	6,737 S	78.8	47.7	4.6 (amino acids)
				6-10		99.5		4,671 F	54.7	41.7	
				14-18		98.8		4,819 F		39.5	8.6 (plasma)
				21-25		98.0		2,339 F	27.4	21.7	
B. W. F 58 yr.	9	4	Hand, forearm, shoulder and chest	3-7	63.6	100.2	1,257.6	4,268 S	67.1	26.0	.....
				10-11		101.1		4,268 S		22.5	
C. L. F 32 yr.	10	1	Face, forearms, shoulders and hands	1-5	77.7	101.6	1,485.6	4,556 S	58.6	36.7	4.6 (plasma)
				6-10	77.2	100.7		3,000 S	38.6	29.8	
				11-15	77.9	99.1		3,000 S		29.8	
				16-20	77.0	99.0		3,353 E & F		30.7	
				26-30		98.6		2,876 F		23.0	
P. R. F 32 yr.	18	0	Face, thighs, hands and arms	3-7	....	100.9	1,533.6	6,350 S	76.6	29.7	.....
				8-13		99.4		3,448 S	41.6	23.7	
				14-17	82.9	98.8		3,563 F		29.8	
D. B. F 16 yr.	63	At least half of body	Back, legs, arms, face and chest	1-4	....	101.2	.....	4,313 S	....	27.6	12.2 (plasma plus whole blood)
F. H. F 17 yr.	64	At least half of body	Arms, legs, back, thorax, face, neck, buttocks and abdomen	1-5	53.2	102.1	1,334.4	3,951 S	74.3	24.6	9.4 (plasma)
				6-7		103.3		3,973 S		28.5	

Average Daily Volume of Urine, Cc.	Nitrogen Output, Gm. per Day					Nitrogen Balance (Excluding Nitrogen Administered as Blood or Plasma)	Comments
	Urine	Feces	Wound	Emesis	Total		
				A			
1,228	20.9	1.2	2.7	...	24.8	—14.9	Gasoline fire burns; left hand healed in 15 days; grafts on right hand and forearm on 25th day, with 100% take
1,210	18.9	0.5	1.3§		20.7	— 8.9	
1,000	14.7	2.4	1.4		18.5	— 7.0	
1,070	11.4	2.7	1.4		15.5	— 4.7	
1,350	10.7	1.2	0.7§		12.6	— 1.7	
1,100	13.0	0.7	2.0	...	15.7	— 6.6	Chronic alcoholism; fire burn; grafts on third degree areas on 25th day
970	12.5	0.8	2.4		15.7	— 6.1	
840	11.5	0.5			12.0	— 2.1 ‖	
1,000	10.5	1.0			11.5	— 1.9 ‖	
3,560	18.3	1.5	3.4	...	23.2	—13.4	Gasoline fire burn; complete healing by 10th day; patient received 96 rat units of antuitrin G ¶ on 2d, 3d, 5th, 6th, 7th, 9th and 10th days
2,450	21.1	1.8	0.2		23.1	—13.7	
3,010	20.6	1.5	...	0.7	22.8	—14.0 ‖	Chronic alcoholism; fire burn; burns deep; patient died on 62d day
2,688	20.3	1.5		0.9	22.7	—11.7 ‖	
2,210	19.6	0.9			20.5	— 9.2 ‖	
3,740	22.1	1.3			23.4	— 4.0 ‖	
3,160	18.4	3.9	...	...	22.3	— 7.4 ‖	Fire burn; deep 2d degree burns which healed without grafting in 35 days
3,990	14.9	2.4			17.3	— 2.5 ‖	
3,740	16.8	3.8			20.6	— 6.7 ‖	
3,650	14.0	Lost		0.3			
1,513	13.4	Lost					
1,500	13.8	Lost					
1,520	12.4	1.5			13.9	+ 3.3 ‖	
1,420	22.6	0.4	7.9	...	30.9	—22.5	Fire burns; patient died at end of 10th day
1,610	19.6	0.4	4.6		24.6	—13.8	
1,480	5.9	0.7	1.8	...	8.4	— 1.0	Fire burn; grafts on 37th day, with 50% take
1,480	5.9	1.4	1.6		8.9	— 0.1	
1,200	5.4	1.4	0.6		7.4	— 1.7	
2,020	15.4	2.3	1.2	0.9	19.8	— 7.3	Fire burn; patient 2 months pregnant; wound healed in 15 days except area on forehead, which required grafting
2,030	23.2	0.7	0.2		24.1	— 3.6	
1,970	22.6	1.5			24.1	— 2.5 ‖	
4,660	10.7	No feces	...	...	10.7	— 2.9 ‖#	Scalded; burns healed by 20th day, except the areas of third degree burns; grafts on 31st day, with 95% take
3,890	13.6	0.7			14.3	— 0.3 ‖	
2,980	14.7	0.7			15.4	— 7.5 ‖	
3,040	12.6	1.4			14.0	— 6.2 ‖	
3,020	9.8	1.3			11.1	— 3.1 ‖	
2,430	9.0	0.5			9.5	— 2.3 ‖	
2,500	10.5	2.4	...	0.1	13.0	+ 4.7 ‖	Fire burn; patient died 2d day
				B			
1,210	12.6	6.6	1.8	1.4	22.4	+ 3.0	Burns with hot grease; deep second degree burns, which did not heal until 35th day
1,410	14.3	3.1	1.2	0.3	18.9	+ 7.4	
2,010	15.9	1.8	0.7		18.4	+ 1.9	
1,840	16.5	2.0	0.4		18.9	+ 1.6	
2,100	16.6	2.0			18.6	+ 1.2 ‖	
1,600	16.0	2.2		0.1	18.3	+ 5.1 ‖	
1,580	15.6	2.3			17.9	+ 3.1 ‖	
.....	30.6	4.3	...	6.2	41.1	+ 4.6 ‖	Flash burn (illuminating gas)
	27.0				27.0	+14.7 ‖#	
	26.0				26.0	+13.5 ‖#	
	23.8				23.8	— 2.1 ‖#	
1,300	20.8	1.8	...	0.6	23.2	+ 2.8 ‖	Fire burn; elderly, mentally confused and incoherent patient, with extremely deep burns; died on 13th day
1,300	18.4	2.4		0.3	21.1	+ 1.4 ‖	
2,140	24.8	5.8	...	0.04	30.6	+ 6.1 ‖	Flash burn (illuminating gas); facial burns healed in 10 days; other areas healed by 20th day except for dorsal aspects of both hands, which were grafted on 23d day, with 100% take
2,750	27.7	1.9		0.1	29.7	— 0.1 ‖	
2,680	29.3	2.0			31.3	— 1.5 ‖	
2,670	22.8	3.8			26.6	+ 4.1 ‖	
2,390	17.7	1.7			19.4	+ 3.6 ‖	
1,260	21.2	3.7	...	1.9	26.8	+ 2.9 ‖	Flash burn (illuminating gas); nearly healed on 17th day
2,200	23.2	3.3		1.0	27.5	— 3.8 ‖	
1,725	21.2	3.3			24.5	+ 5.3 ‖	
1,952	23.2	2.9	...	0.3	26.4	+ 1.2 ‖	Flash burn (illuminating gas); patient died on 5th day
3,170	23.5	1.2	...	0.3	25.0	— 0.4 ‖	Fire burn; patient received 96 rat units of antuitrin G ¶ daily; died on 7th day
2,475	30.6	1.0		0.3	31.9	— 3.4 ‖	

Patient; Sex; Age	Per Cent of Body Burned: Total	Per Cent of Body Burned: 3d Degree	Location	Days After Burn	Weight in Kg.	Average Temperature per Period, F.	Estimated Basal Caloric Requirement *	Caloric Intake per Day †	Calories per Kg. per Day ‡	Nitrogen Intake, Gm. per Day: Oral	Nitrogen Intake, Gm. per Day: Parenteral
					C						
L. A. M. 12 yr.	12	10	Both legs	1-5	40.7	100.5	3,193.6	3,864 S	94.9	25.0	.....
				6-10		100.7		3,684 S		23.5	
				11-15		99.2		2,358 F	57.9	17.1	
				16-20		99.2		2,030 F		15.6	
				24-28		99.4		2,054 F		16.0	
				29-33		98.3		1,992 F	48.9	15.7	
					(admission 34.1)						
G. R. M. 10 yr.	26	22	Both legs and left hand	1-5	33.2	100.4	1,140.0	3,500 S	102.6	19.9	1.6 (plasma)
				6-10	33.4	101.3		3,173 S		16.9	
				11-15	28.6	99.7		3,500 F		19.4	
				16-23		99.0		1,671 F	49.0	13.8	
				26-30	30.0	100.6		1,681 F		14.2	
				31-35	30.4	100.9		1,695 F		13.9	
				36-39	28.9	99.2		1,695 F		13.6	2.6 (blood)
I. S. F 5 yr.	5	5	Back, axilla and right arm	1-5	....	100.4	691.2	1,061 F	70.7	4.8	.....
				6-10		100.0		1,193 F		4.5	
				11-15		100.3		1,136 F		5.2	
				16-20		99.7		1,108 F		4.9	
				24-29	15.0	98.7		984 F		4.9	
				30-34		98.2		783 F	52.2	4.6	
					(admission 17.5)			600 S)			
D. H. F 5 yr.	9	9	Right half of back and right hip	1-5	18.2	100.9	746.4	1,133 E)**††	52.6	4.7	1.6 (plasma)
				6-10	18.6	101.8		1,133 E	64.7	7.9	
				11-15	17.5	99.9		1,175 E		9.6	
				16-20	17.0	99.8		1,175 E		9.4	
				21-25	16.6	99.3		1,152 E		7.8	
				36	17.9						
L. W. F 10 yr.	14	10	Right side of trunk	1-5	23.4	101.2	800.4	1,824 S	77.9	10.0	5.0 (plasma)
				6-10	23.4	101.2		1,893 S		11.0	
				11-15		100.8		1,890 S		10.8	
				16-20	21.4	100.9		2,117 S	90.5	15.3	
D. R. F 12 yr.	15	Less than 0.5%	Back, arm and buttocks	1-5	40.9	100.3	1,226.4	2,760 F	67.5	16.1	1.3 (plasma)
				6-10		99.8		2,764 S		16.4	
				11-15	42.7	98.5		2,995 S	73.2	16.4	

* Estimated basal caloric requirement computed on basis of weight by the formula of Dreyer (The Normal Basal Metabolism in Man, Lancet **2**: 289-291, 1920).

† Total calories per day calculated from food tables. F indicates a diet of conventional food; S, a synthetic diet, and E, a diet of eggnog and orange juice.

‡ Calculated on basis of patient's weight on admission to the hospital.

§ Not a complete collection.

ment, the patient's age and sex, the type of burn and the extent and nature of the shock therapy employed.

The nitrogen lost in the exudate from the burn was measured for 12 patients. The significance of this loss was discussed in detail in a previous communication.[6] It varied from 7.9 Gm. per day during the first five days in C. W., an adult man whose body surface was 33 per cent burned, to 0.7 Gm. per day for the first five days in I. S., a 5 year old girl whose body surface was 5 per cent burned. In general, the nitrogen content of the exudate from the wound was highest during the first few metabolic periods. It then remained fairly constant unless the burned area decreased in size through spontaneous healing or skin grafting.

The question naturally arose as to whether the nitrogen deficit could be prevented or diminished by feeding diets of high carbohydrate and protein content. In an attempt to answer this question, a number of patients were given a diet containing 54 to 102 calories per kilogram of body weight. The protein content varied from 1.25 to 3.6 Gm. per kilogram.

In contrast to the patients on a diet low in calories and nitrogen, the patients who succeeded in retaining a high caloric and nitrogen intake maintained, or nearly maintained, their weight, and they lost only small amounts of body protein, as evidenced by a slight nitrogen deficit (sections B and C of table). One patient (A. M.) actually retained nitrogen during the entire period of study, while others were periodically in positive nitrogen balance. The patients with high caloric and nitrogen intakes who were in negative nitrogen balance came into positive balance much sooner than the patients with the lower caloric and nitrogen intakes. Clinically the state of nitrogen balance had no perceptible effect on the rate of wound healing during the time the patients were studied under the experimental regimen.

Although it was possible by means of a high caloric and protein intake to prevent excessive loss of nitrogen and weight, the clinical course of these patients seemed to leave little doubt that forced feeding with the type of diet employed is undesirable, at least during the first ten days after injury.

COMMENT

It has been known for a long time that patients suffering with an acute infectious disease excrete abnormally large amounts of nitro-

Three Patients with Thermal Burns—Continued

Average Daily Volume of Urine, Cc.	Nitrogen Output, Gm. per Day					Nitrogen Balance (Excluding Nitrogen Administered as Blood or Plasma)	Comments
	Urine	Feces	Wound	Emesis	Total		
					C		
1,390	19.7	0.6	2.1	2.0	24.4	+ 0.6	Fire burn; grafts on 22d day
1,470	21.7	0.7	1.2	1.5	25.1	— 1.6	
2,160	19.7	1.3	1.8		22.8	— 5.7	
2,520	15.0	1.3	1.8		18.1	— 2.5	
2,340	13.9	2.0			15.9	+ 0.1 ‖	
1,820	12.3	2.1			14.4	+ 1.3 ‖	
880	15.4	0.6	2.6	4.8	23.4	— 3.5	Fire burn; grafts on 25th day, with perfect take; patient received 96 rat units of antuitrin G ¶ on 1st, 2d, 3d, 4th, 5th, 6th, 7th, 8th and 9th days
1,320	17.7	1.4	2.0	6.0	27.1	—10.2	
1,460	16.4	1.2	2.3	4.1	24.0	— 4.6	
1,600	12.6	1.0		1.3	14.9	— 1.1 ‖	
970	9.9	1.6			11.5	+ 2.7 ‖	
1,000	7.4	1.2		1.1	9.7	+ 4.2 ‖	
1,125	10.1	0.9		1.1	12.1	+ 1.5 ‖	
710	5.7	1.0	0.7	...	7.4	— 2.6	Fire burn; grafts on 20th day, with complete take
780	5.0	0.4	0.9		6.3	— 1.8	
1,140	4.6	1.1	0.8		6.5	— 1.3	
1,070	4.4	0.7	0.8		5.9	— 1.0	
990	3.5	1.2			4.7	+ 0.2 ‖	
810	3.4	0.6			4.0	+ 0.6 ‖	
1,400	5.1	0.3	1.0	...	6.4	— 1.7	Fire burn; grafts on 27th day, with excellent take
1,300	7.5	0.5	1.1		9.1	— 1.2	
1,460	6.6	0.6	1.2		8.4	+ 1.2	
1,420	7.2	0.3	1.2		8.7	+ 0.7	
1,020	4.6	0.4			5.0	+ 2.8 ‖	
1,620	11.0	0.6	...	1.6	13.2	— 3.2 ‖	Fire burn; grafts on 25th day, with 90% take, and on 44th day, with 95% take
1,240	11.5	1.9			13.4	— 2.4 ‖	
900	9.4	2.2		0.5	12.1	— 1.3 ‖	
890	10.1	1.7		1.7	13.5	+ 1.8 ‖	
2,240	11.5	2.9	2.5	0.3	17.2	— 1.1	Fire burn; healed in 15 days except for a small area that required grafting, which was done on 16th day
3,250	17.5	1.7	1.4		20.6	— 4.2	
4,130	16.4	1.5	0.6		18.5	— 2.1	

‖ Does not include nitrogen lost from wound.
¶ A preparation containing the growth-promoting (somatotropic) principle derived from the anterior lobe of the pituitary.
# Does not include fecal nitrogen.
** Synthetic diet (no nitrogen was administered orally on first two days).
†† Average 930.

gen in the urine and are in negative nitrogen balance. This has been attributed to the toxic destruction of body protein by bacterial products or to the toxic effect of the breakdown products of injured tissue. Shaffer and Coleman,[10] in 1909, studied this phenomenon in patients with typhoid. They concluded that the loss of nitrogen during the febrile period of this disease could be prevented or compensated for "by the use of diets of high caloric value and especially rich in carbohydrate." Although Shaffer and Coleman apparently were able to decrease the nitrogen loss in patients with typhoid by feeding a diet containing large amounts of carbohydrate, they succeeded in obtaining nitrogen equilibrium in only 1 patient during the early stage of the disease, and then for just a few days. In later studies Coleman and DuBois[11] demonstrated that patients with typhoid could not be kept in nitrogen equilibrium with a caloric intake sufficient to cover their energy requirements. These authors concluded that it was necessary to provide calories 50 to 110 per cent in excess of the energy requirement in order to obtain a positive nitrogen balance. Even with these large caloric intakes it was not possible to reduce the protein metabolism of patients with typhoid to the low level that can be obtained for normal persons[10] on a similar diet. To obtain nitrogen equilibrium it was necessary, in spite of a high caloric intake, to provide 10 to 15 Gm. of nitrogen in the diet. The conclusion seemed inescapable that typhoid increases the rate of protein catabolism.

Cuthbertson[12] observed that similar alterations of protein metabolism occur after fracture and other types of trauma. In a study of the metabolic disturbances following fracture he[13] concluded that it was possible with diets high in carbohy-

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11. Coleman, W., and DuBois, E. F.: Calorimetric Observations on the Metabolism of Typhoid Patients With and Without Food, Arch. Int. Med. **15**:887-938 (May) 1915; The Influence of the High-Calory Diet on the Respiratory Exchanges in Typhoid Fever, ibid. **14**:168-209 (Aug.) 1914.

12. Cuthbertson, D. P.: Post-Shock Metabolic Response (Arris and Gale Lecture), Lancet **1**:433-436, 1942.

13. Cuthbertson, D. P.: Further Observations on the Disturbance of Metabolism Caused by Injury, with Particular Reference to the Dietary Requirements of Fracture Cases, Brit. J. Surg. **23**:505-520, 1936.

drate and protein to decrease the nitrogen loss during the early period after injury but that it was not possible to obtain a positive nitrogen balance. Cope and his co-workers,[14] on the other hand, stated that it was not difficult to obtain a positive nitrogen balance in burned patients of the Cocoanut Grove disaster when the caloric and nitrogen intake was adequate. A review of their data shows that nitrogen equilibrium was accomplished largely with the use of plasma or blood. It was not accomplished in the early period after injury with food alone. Furthermore, the nitrogen lost in the stools and the exudate was not included by Cope and his co-workers in constructing their tables. One can speculate, therefore, whether most of the patients would not have been in negative nitrogen balance if they had not received large amounts of blood and plasma and if the nitrogen lost from the wounds and in the stools had been considered.

The present data confirm the results of other workers[15] who have found that burned patients excrete large amounts of nitrogen in the urine. The results seem to show also that it is possible to overcome, or at least to diminish, this loss by giving a diet of high carbohydrate and protein content. In practice this is attended with considerable difficulty in the first few weeks after injury because the patients have poor appetites. Whether or not it is desirable or necessary to give normal or slightly increased quantities of food during the acute phase of a burn is not known. There is no doubt, however, that it is necessary at the end of a week or ten days if the patient has an extensive third degree burn. Such a patient faces a prolonged period of illness; and if he is not forced to take food, protein and vitamin deficiencies develop.

More work is required to demonstrate whether this abnormal nitrogen loss in burned patients can be compensated for by the administration of large amounts of protein without the high caloric intake employed. If this is possible, it would be more practical.

The mechanism of the protein loss in these patients has not been definitely established. Albright[16] and Browne[17] expressed the opinion that it is due to a change in adrenal cortex hormone production and is a pattern of response which the body makes to all types of injury (alarm reaction), as described by Selye.[18]

Until the cause of the undesirable effects we observed is determined, it seems wiser not to force food on burned patients during the acute phase but, rather, to provide them only with such food as they desire and can tolerate. Attempts to force large quantities of food at this time apparently result in upsetting the patient. After two or three days have passed, he can be given a moderate diet. If the patient has a severe burn and faces a prolonged convalescence, it is essential to increase the diet as rapidly as can be tolerated, especially in regard to its protein content.

SUMMARY

The nitrogen balance of 23 burned patients was determined by comparing the nitrogen intake with the nitrogen lost in the vomitus, urine, feces and exudate from the wound.

All the patients excreted large amounts of nitrogen in the urine, and, except for a few who received abnormally large quantities of protein and carbohydrate, were in negative nitrogen balance and lost considerable weight.

It was possible to prevent or decrease a negative nitrogen balance and to prevent or diminish loss of weight by feeding diets of high protein and caloric content. However, the diets employed in this study were poorly tolerated during the first few days after injury.

Most burned patients, if allowed to eat only what they desire, will not consume an adequate diet. It is important therefore, after the shock phase of the injury has passed, to insist that they eat sufficient food to maintain proper nutrition.

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Research Laboratory of the Children's Fund of Michigan, Wayne University College of Medicine.

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15. Davidson.[1] Footnote 2.

16. Albright, F.: Cushing's Syndrome. Its Pathological Physiology; Its Relationship to the Adrenogenital Syndrome, and Its Connection with the Problem of the Reaction of the Body to Injurious Agents ("Alarm Reaction" of Selye), in Harvey Lectures, 1942-1943, Lancaster, Pa., Science Press, 1943, vol. 38, pp. 123-186.

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18. Selye, H.: The Alarm Reaction, in Piersol, G. M.; Bortz, E. L., and others: Cyclopedia of Medicine, Surgery and Specialties, Philadelphia, F. A. Davis Company, 1940, vol. 15, pp. 15-38.

INFLUENCE OF ENVIRONMENTAL TEMPERATURE ON SHOCK

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LOS ANGELES

A number of experimental observations on the effect of environmental temperature on shock have recently been made.[1] It was observed that extremes of heat and cold have deleterious effects on the survival time of animals in shock.[1a, b] There have been wide differences of opinion as to the optimal environmental temperatures for shocked persons. Thus, Elman and his coworkers [1c] recommended a temperature of 75 F., Cleghorn [1d] 72 F. and Wakim and Gatch [1e] 85 F. Examination of the data presented by the various authors shows that these variations may be due to study of an insufficient number of temperatures in the region of 65 to 95 F. Likewise, the number of animals employed may not always have been adequate for demonstrating significant responses with small differences in temperature.[2] It is the purpose of this report to determine in a more complete manner the optimal temperature for decreasing mortality in mice subjected to burn shock and to report observations on the possible mechanism of the effects observed.

The altered hemodynamics in burn shock have recently been studied in this laboratory.[3] It has been found that the reduced circulating blood volume in burn shock is due to two separate factors, capillary atony and local fluid loss. By transfusion experiments, it was shown that there is a toxic factor in the blood of burned animals which produces capillary atony. The capillary atony is characterized by an increase in number and diameter of open capillaries. For example, over three times as many open and dilated capillaries were counted in the kidneys of burned rats as in those of nonburned animals. Likewise, there were approximately five times as many open capillaries in the hearts of shocked animals as there were in the hearts of control animals.[4] This capillary atony, which causes intense congestion of the viscera, is not due to heart failure or to anoxia, since it was shown that capillary congestion begins immediately after severe trauma. Measurement of the hemoglobin retained by the viscera of shocked animals showed an increase in blood content over that of nonburned animals. In these experiments, both control and shocked animals were killed by exsanguination. This was necessary since it was found that if the animals were not exsanguinated, the appearance of the shocked organs was not particularly distinctive. The relative importance of local fluid loss and the toxic factor varied with the character of the burn and the time after trauma. In certain types of burns the factor of local fluid loss was unimportant and the capillary toxic factor accounted for all disturbances. Under other conditions the factor of local fluid loss was operative in the first few hours after trauma but the toxic factor became progressively more significant and later dominated the clinical picture. Likewise, in shock produced by a muscle-crushing injury in dogs,[5] in which infection is of primary importance, further experi-

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mentation demonstrates that the same two factors also operate in causing the shock state: the capillary toxic factor, which appears to be most important, and varying degrees of local fluid loss. Preliminary observations made in this laboratory on tourniquet shock indicate that these two factors are also involved in the resulting shock state. The prophylactic effectiveness of liver extract and other compounds has recently been studied in this manner.[6] The quantitative and qualitative data on the cause of the decreased circulation in shock make possible the application of the same methods to determine reasons for the deleterious influence of certain environmental temperatures on the mortality of burned mice.

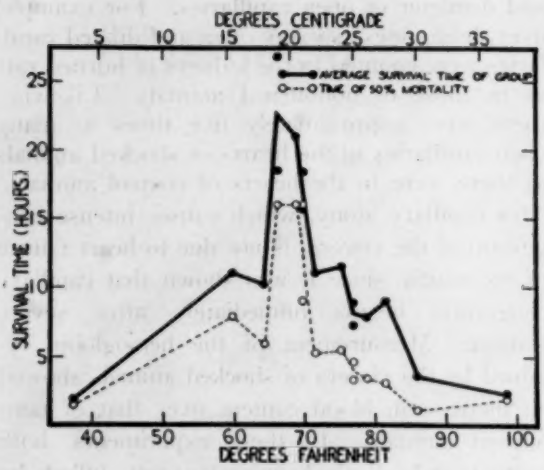
DEGREES CENTIGRADE
5 10 15 20 25 30 35
AVERAGE SURVIVAL TIME OF GROUP
TIME OF 50% MORTALITY
SURVIVAL TIME (HOURS)
25 20 15 10 5
40 50 60 70 80 90 100
DEGREES FAHRENHEIT

Chart 1.—Effect of environmental temperature on mortality in burn shock. Each point represents 20 to 26 mice, etherized and scalded up to the head at 65 C. for ten seconds, kept in rooms at various constant temperatures. The range of environmental temperatures for optimal survival is 65 to 71 F.

EXPERIMENTAL STUDIES

EXPERIMENT 1.—*Effect of environmental temperature on mortality in burn shock.*

Groups of 20 to 26 mice, completely anesthetized with ether and burned up to the head in water at 65 C. (149 F.) for ten seconds, were placed in various rooms at different temperatures. This severe burn causes high mortality, with typical clinical and pathologic manifestations of shock.[2] Each room was maintained at a constant temperature throughout a forty-eight hour period of observation. The mice alive at the end of this period were arbitrarily assigned a survival time of forty-eight hours. In confirmation of the results of others, it was immediately apparent that extremes of heat (98 F.) and of cold (37 F.) were associated with a great increase in mortality. We therefore performed most of our experiments at temperatures between 60 and 85 F. A total of 399 mice were used to obtain the data represented in chart 1. It can be seen that the optimal temperature range for survival is between 65 and 71 F. At 75 F. the mortality is definitely higher than at 71 F. At 85 F. most of the animals died rapidly.

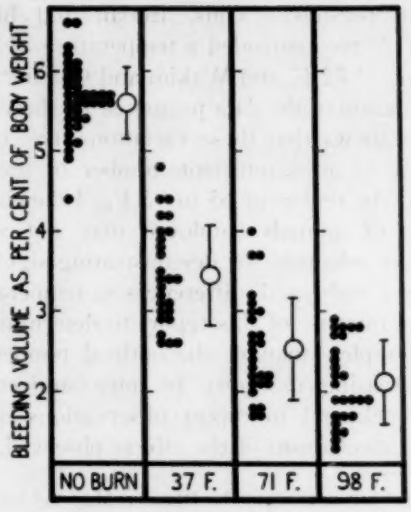

Chart 2.—Effect of environmental temperature on bleeding volume. Mice anesthetized and burned up to the head at 61 C. for ten seconds were divided into three groups and placed in rooms at 37, 71 and 98 F. respectively. Bleeding volumes were taken from one-half hour to two hours after trauma. Each dot represents the bleeding volume of 1 mouse. The large circles represent the mean response; the total length of the vertical lines equals two times the standard deviation of a single observation; the small horizontal lines at the ends of the vertical lines have a length equal to the standard error of the mean. It can be seen that the bleeding volume of shocked animals kept at ordinary room temperature (71 F.) is reduced as compared with that of nonshocked animals. There is a further reduction of the bleeding volume of burned animals kept at 98 F. The reduction of the bleeding volume at 37 F. is significantly less than at 71 F.

EXPERIMENT 2.—*Effect of environmental temperature on bleeding volume.*

Determinations of bleeding volumes were made on burned mice placed in three different environmental temperatures (37, 71 and 98 F.), in an effort to determine in what manner external temperature influences mortality. The method of

6. Bergman, H. C., and Prinzmetal, M.: The Prevention of Burn Shock and the Reduction of Inflammatory Edema with Liver Extract, Morphine, Pentobarbital and Ethanol, to be published.

determining bleeding volume has been previously described.[3] Briefly, it consists in removing the heart of etherized animals and mopping up the blood in the thorax with a weighed cotton pledget until the return flow of blood has ceased. This procedure requires about two to four minutes. It can be seen in chart 2 that a sharp reduction occurs in bleeding volume of burned animals subjected to a hot environment (98 F.) as compared with that of animals subjected to ordinary room temperature (71 F.). We were somewhat surprised to observe that in spite of the increased mortality of burned mice subjected to cold (37 F.) over that of burned mice at ordinary room temperature, the bleeding volumes of mice in the cold environment were reduced less than the bleeding volumes of mice at ordinary room temperature. It is reasonable to suppose that the increased mortality in the hotter environments can be attributed to the further reduction in effective circulation, with subsequent accentuation of the shock. But the increased mortality in cold environments cannot be attributed to this physiologic change. Efforts to find the possible cause of this increased mortality will be presented later.

EXPERIMENT 3.—*Effect of environmental temperature on the toxic factor and capillary atony.*

The amount of blood remaining in an organ after exsanguination of a shocked animal measures the degree of capillary atony which is caused by the toxic factor.[3] The amount of blood retained in the kidneys and livers was determined on three groups of burned mice at external temperatures of 37, 71 and 98 F. and on an equivalent group of nonburned mice. The hemoglobin content of the organs was estimated colorimetrically after extraction of the macerated tissues with 20 per cent urea solution with frequent shaking for twenty-four hours at ordinary room temperature; 10 cc. of urea solution was taken for each gram of tissue. Values for hemoglobin obtained by this method are only semiquantative, as indicated by work now in progress in our laboratory. The amount of hemoglobin retained after exsanguination in the kidneys and livers of burned mice kept at 37, 71 and 98 F. for three and one-half to four and one-half hours as compared with that retained by nonburned exsanguinated mice is shown in chart 3. It can be seen that there is an increased amount of hemoglobin in the organs of shocked animals in comparison with those of control animals, confirming our previous observations.[3] It can also be seen that the degree of capillary atony, as measured by the hemoglobin content, is further increased when animals are kept at the hot environmental temperature. In the cold, on the other hand, there is a decrease in the degree of visceral congestion as compared with the congestion at ordinary room temperature.

EXPERIMENT 4.—*Effect of environmental temperature on local fluid loss.*

One hindlimb of 78 etherized mice was scalded at 65 C. (149 F.) for ten seconds. The animals were divided into three groups of 26 animals each and placed in environmental temperatures of 37, 71 and 98 F. respectively. The mice were killed three and one-half to four and one-half hours later by exsanguination under ether anesthesia. The amounts of local fluid loss and bleeding volumes

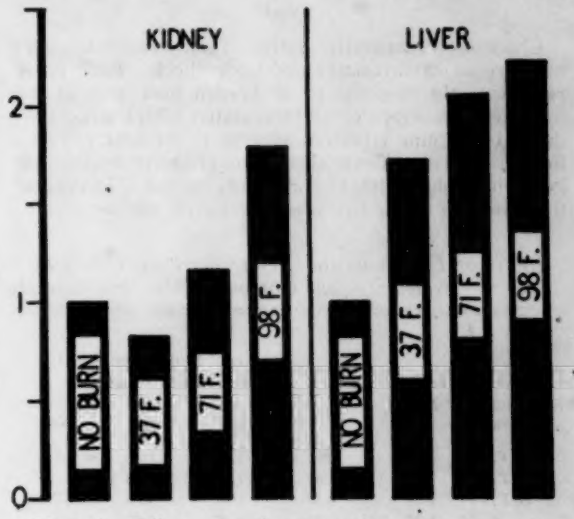

Chart 3.—Effect of environmental temperature on the degree of congestion in the kidneys and livers of burned mice. The results illustrated were obtained on the same mice for which data are presented in chart 2, equal masses of tissue being compared. Less hemoglobin was retained after exsanguination in the kidneys and livers of burned mice kept at 37 F. than at 71 F. More hemoglobin appeared after exsanguination in the kidneys and livers of burned mice kept at 98 F. than at 71 F. The latter results show a further increase in capillary atony in shocked mice exposed to a high external temperature. The numbers at the left indicate hemoglobin retention.

were determined. The method for estimating the degree of local fluid loss has been presented elsewhere.[7] This is a modification of Blalock's bisection method.[8] It can be seen from the table

7. Prinzmetal, M.; Bergman, H. C., and Hechter, O.: A Demonstration of Two Types of Burn Shock, Surgery **16**:906-913, 1944.

8. Blalock, A.: Experimental Shock: VII. The Importance of the Local Loss of Fluid in the Production of Low Blood Pressure After Burns, Arch. Surg. **22**: 610-616 (April) 1931.

that no significant difference in the degree of local fluid loss occurred in the environmental temperatures studied but the same relative changes in toxic factor and bleeding volume occurred after a burn involving 90 per cent of the body surface (charts 2 and 3). It must be realized that the entire animal was placed at these temperatures, and it is possible that if the burned area alone had been subjected to heat or cold the degree of local fluid loss might have been influenced.[9]

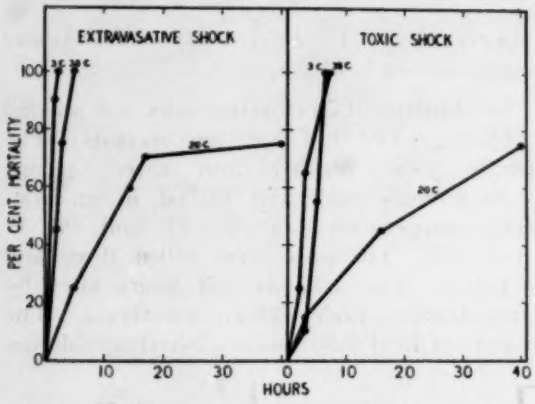

Chart 4.—Comparative effect of environmental temperature on extravasative and toxic shock. Each curve represents the response of 20 burned mice kept at the indicated temperature. Extravasative shock was produced by burning etherized mice up to the head at 65 C. for ten seconds. Toxic shock was produced by burning both hindlimbs at 100 C. for twenty seconds. In general the responses to the two procedures were similar.

EXPERIMENT 5.—*Effect of environmental temperature on extravasative and toxic shock.*

It has been previously shown that animals may die in shock with or without local fluid loss, depending on the character of the burn.[7] In rats and mice, burns at 100 C. (212 F.) for twenty seconds produce little or no local fluid loss and death is due entirely or almost entirely to the toxic factor. Burns at 65 C. for ten seconds, on the other hand, produce appreciable local fluid loss, which, together with the capillary toxic factor, causes a reduction in effective circulation. We are now attempting to determine whether these factors are operative in human injuries.

In connection with the present problem, it was felt important to know whether the factor of environmental temperatures which influence the mortality of mice with burns producing local fluid loss was likewise operative in mice with burns without local fluid loss. Toxic burn shock was produced in 60 etherized mice by scalding both hindlimbs at 100 C. for twenty seconds. The animals were divided into three groups of 20 mice each and placed in environmental temperatures of 37.4, 68.0 and 100.4 F. respectively. These groups were compared with equal numbers of mice scalded up to the head at 65 C. for ten seconds and placed in these various environmental temperatures at the same time. It can be seen in chart 4 that the general character of the time-mortality curves is the same in both types of burn. This experiment presents additional evidence that the deleterious effect of environmental temperature is not due to an effect on local fluid loss, since, as shown in this experiment, a similar effect on mortality occurs irrespective of local fluid loss.

Effect of Environmental Temperature on Etherized Mice with One Hindleg Scalded at 65 C. for Ten Seconds; Data Obtained Three and One-Half to Four and One-Half Hours After Trauma

Environment Temperature	No. of Mice	Local Fluid Loss (Per Cent Body Weight)				Bleeding Volume (Per Cent Body Weight)				Hemoglobin Retention (Ratio of Treated to Nontreated)	
			SD *	SE †	SR ‡		SD	SE	SR	Liver	Kidney
37 F.	26	3.94	1.15	0.23	2.6	4.51	0.73	0.14	2.0	0.87	1.06
71 F.	26	4.82	1.20	0.24	...	4.08	0.80	0.16	...	1.15	1.09
98 F.	26	4.13	0.92	0.18	2.3	3.55	0.86	0.17	1.8	1.29	1.38
No burn	12	0.39§	0.25	0.07	...	....	....	....	...	1.00	1.00
	37	....	....	....	...	5.63	0.45	0.07			

* Standard deviation of a single observation.
† Standard error of the mean.
‡ Significance ratio, compared to 71 F.
§ The percentage difference in quadrant weight of 12 nonburned animals.

COMMENT

An optimal temperature range for survival of shocked mice has been found to be 65 to 71 F. Small changes in temperature above or below this range cause a striking increase in mortality. It would appear to be of greatest importance to determine whether this general situation holds

9. Allen, F. M.: Resistance of Peripheral Tissues to Asphyxia at Various Temperatures, Surg., Gynec. & Obst. **67**:746-751, 1938.

true for human beings. It has been suggested that this information could be obtained by making similar observations on anthropoid apes.[10] The difficulties involved in such an attempt become apparent when one considers that in our first experiment it was necessary to use 400 animals to find the optimal temperature range. A priori, it would seem that environmental temperature might have less effect on human beings than on small laboratory animals during equal periods of exposure because of the larger mass involved. However, since it has been shown that environmental temperature influences the mortality of shock with many sorts of animals (dogs, rabbits, guinea pigs, rats and mice), it would seem reasonable to expect similar effects in persons. There is no evidence at present which suggests that the optimal temperature range for lowest mortality is different for human beings, and until contrary evidence is obtained it would seem advisable to accept these data as applicable. Operating rooms are often overheated in the winter, and facilities for air conditioning in summer are not always available. Likewise, it has been reported that many of the military operating rooms in the tropics are not air conditioned. In view of our observations, it is easy to see how injury resulting from long traumatizing surgical procedures might in such circumstances be aggravated, and the mortality attributed to so-called surgical shock would be greatly increased. After severe surgical procedures the patient should be placed in a cool room, at 65 to 71 F., until the possibility of further shock has passed. The same principle should apply to the management of other types of trauma which are so frequent in wartime. One exception to this rule should be noted as applying to the treatment of a severely chilled subject, in which case, as observed by Cannon,[11] the temporary application of heat often causes a good restoration of pulse, blood pressure and appearance.

All experiments on the effect of environmental temperature, including our own, have been done on animals without infections and spontaneous fever. It appears possible that these data may not apply in the presence of fever.

The deleterious effect of a hot environment on shock can be adequately explained by the occurrence of a further decrease in blood volume and an increase in capillary atony and visceral congestion, which becomes demonstrable after exsanguination. It is possible that the increased capillary congestion is due to an increased production of the toxic products in the burned area. Heat increases metabolic activity. If a toxic product is a result of a chemical reaction following a burn, then increased amounts should be formed in a warm environment. One could assume that heat increases the blood flow to the burned area, causing greater absorption of the toxic materials. However, although the blood flow to a normal part is greatly increased by heat,[12] it has yet to be shown that this is true for inflamed areas.

The influences of cold on mortality is more difficult to explain. The lessened reduction of bleeding volume and the decreased capillary congestion are compatible with the hypothesis that a lesser concentration of the toxic substance is present in the circulating blood either because less is formed or because less is absorbed. Nevertheless, in spite of this apparent beneficial effect, there is an increased mortality. Since the increased mortality is not due to any known physiologic hemodynamic alteration, it must be due to a yet unknown change. In a few preliminary experiments, we have found that the administration of adrenal cortex extract or solution of dextrose did not influence the increased mortality in a cold environment. Thus, it is unlikely that adrenal exhaustion or hypoglycemia is the cause of the increased mortality. Others [13] have found that the body temperature of animals subjected to cold is noticeably reduced, an observation which we readily confirmed in mice. Crismon [13a] has demonstrated that death from hypothermia in normal rats is due to circulatory and respiratory failure. It would seem likely that temperature regulation is impaired in shocked animals because of the inadequate circulation and the reduced ability to compensate in other ways, such as by vigorous shivering. The deleterious effects of cold should

10. Cooling in Shock, editorial, J. A. M. A. **121**:432-433 (Feb. 6) 1943.

11. Cannon, W. B.: Personal communication to the authors.

12. Prinzmetal, M., and Wilson, C.: The Nature of the Peripheral Resistance in Arterial Hypertension with Special Reference to the Vasomotor System, J. Clin. Investigation **15**:63-83, 1936.

13. (*a*) Crismon, J. M.: Effect of Hypothermia on the Heart Rate, the Arterial Pressure and the Electrocardiogram of the Rat, Arch. Int. Med. **74**:235-243 (Oct.) 1944. (*b*) Blalock and Mason.[1a]

be considered if one attempts to treat the entire body by refrigeration, as recommended for therapeutic use in a variety of ailments.[14]

CONCLUSIONS

1. The optimal environmental temperature range for highest survival of mice in burn shock was found to be 65 to 71 F.

2. In a hot environment, the increased mortality in shock is due to a further decrease in the effective circulation and an increase in capillary congestion caused by the toxic factor.

3. In shocked mice kept in a cold environment, an increased bleeding volume and a reduced degree of capillary atony were found when compared with values obtained in an environment with ordinary room temperature. The cause of the increased mortality in a cold environment is as yet unknown.

4. Environmental temperatures of 37, 71 and 98 F. had no signficant effect on local fluid loss following burns.

14. Smith, L. W.: The Use of Cold in Medicine, Ann. Int. Med. **17**:618-636, 1942.

BLOOD IODINE STUDIES

VI. AN ANALYSIS OF THE BLOOD IODINE IN THYROID DISEASE

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A principal consideration in this series of studies is the relation of the blood iodine level to the basal metabolic rate in various physiologic and pathologic states.

Within recent years there have been an abundance of investigations directed toward the understanding of the nature of blood iodine, and many features have thus been revealed. But as yet its essential composition and the exact relation it bears to the thyroid hormone is unknown. Its clinical value, notwithstanding, has become increasingly apparent, particularly for patients with thyroid disease, for whom the basal metabolic rate alone is inadequate as a diagnostic measure. Its theoretic value in disclosing causal relationships in certain diseases may prove of even greater significance. For these reasons, we have made a comparative analysis of the blood iodine, basal metabolic rate and certain other factors in 138 different clinical conditions in a total of 818 persons. Our earlier blood iodine values, from 1932 to 1936, were determined by the dry ash technic,[1] and the remainder, from 1936 to date, by the chromium trioxide method.[2]

VALUE OF BLOOD IODINE DETERMINATIONS

There are persons who maintain that blood iodine determinations are of questionable clinical value. They feel that the method is too cumbersome to warrant its use, particularly in view of the availability of basal metabolic rate determinations, which they consider not only more practical but sufficiently inclusive, as a laboratory aid in the recognition of changes in thyroid function. What they fail to see, however, is that the two methods should be used side by side, each as a supplement to the other. Nor are analyses of blood iodine now especially cumbersome or lacking in precision.

The blood iodine, and specifically its protein-bound fraction, is an index of the circulating thyroid hormone.[3] As shown by tolerance curves, it is regulated essentially by the functional activity of the thyroid gland.[3a] This is the principal basis for its importance in clinical as well as in experimental studies.

The behavior of the blood iodine, particularly of its organic, or protein-bound, fraction, may prove to be of diagnostic significance in instances in which it is difficult or even impossible to obtain a reliable determination of the basal metabolic rate; also, in the differentiation of hyperthyroidism from other simulating conditions, in which the basal metabolic rate is likewise elevated, as, for example, in patients with hypertension or with cardiac decompensation. Further, it is of value in distinguishing goiter with hyperthyroidism clinically from goiter without hyperthyroidism, in which the basal metabolic rate may be otherwise increased.

Perkin and Cattell have presented convincing evidence that the amount of iodine in the blood may be a more reliable criterion than the basal metabolic rate in the differential diagnosis of borderline hyperthyroidism, so important a decision, especially in the consideration of therapy.[4] In a study of 235 patients with borderline hyperthyroidism under carefully controlled conditions, they found that despite a generally elevated basal metabolic rate the blood iodine level was not significantly increased in the majority of persons for

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Aided by a grant from the Comly Fund for Research of the Ohio State University.

1. Davis, C. B., and Curtis, G. M.: Blood Iodine Studies: I. The Quantitative Determination of the Iodine Content of Blood, J. Lab. & Clin. Med. **18**:24, 1932. Phillips, F. J., and Curtis, G. M.: Blood Iodine Studies: IV. The Clinical Determination of Iodine in Blood, Urine and Feces, Am. J. Clin. Path. **4**:346, 1934.

2. Matthews, N. L.; Curtis, G. M., and Brode, W. R.: Determination of Iodine in Biological Materials: Refinements of the Chromium Trioxide Oxidation Method, Indust. & Engin. Chem. **10**:612, 1938.

3. (*a*) Salter, W. T.: The Endocrine Function of Iodine, Cambridge, Mass., Harvard University Press, 1940. (*b*) Salter, W. T., and Bassett, A. M.: A Physiological Interpretation of Blood Iodine Fractions in Terms of Thyroid Function (in One Hundred Cases), Tr. A. Am. Physicians **56**:77, 1941. (*c*) Man, E. B.; Smirnow, A. E.; Gildea, E. F., and Peters, J. P.: Serum Iodine Fractions in Hyperthyroidism, J. Clin. Investigation **21**:773, 1942.

4. Perkin, H. J., and Cattell, R. B.: The Value of Blood Iodine Estimations in the Diagnosis of Borderline Hyperthyroidism, West. J. Surg. **48**:50, 1940.

whom a tentative diagnosis of mild hyperthyroidism was unsupported by the clinical observations or in most of those patients with nodular or exophthalmic goiter who subsequently did not benefit by subtotal thyroidectomy. On the other hand, both the basal metabolic rate and the blood iodine level for the most part were elevated preoperatively and declined postoperatively in those who improved clinically after an adequate thyroidectomy.

From a further investigation of 256 patients with exophthalmic goiter, Perkin and Hurxthal concluded that estimations of the blood iodine level taken at stated intervals offer a means whereby predisposition to recurrence or persistence of clinical hyperthyroidism can be predicted.[5] Moreover, the level of the blood iodine may be used as an index for determining the correct amount of thyroid tissue to remove,[6] thus diminishing materially the postoperative complications of hypothyroidism or recurrent hyperthyroidism.

Similarly, Salter and Bassett found that the clinical diagnosis is better correlated with the plasma protein–bound iodine than with the basal metabolic rate.[3b] On the basis of his work, Salter concluded that Graves' disease may exist without physiologic hyperthyroidism.[3a,b]

The determination of the blood iodine may also prove of value for patients with ovarian struma, with total intrathoracic goiter or with other aberrant thyroid tissue, which may be otherwise overlooked. Further, its estimation, as well as that of the urinary output of iodine, will furnish useful evidence in the detection of temporarily induced hyperthyroidism from secretly ingested desiccated thyroid.[7]

The blood iodine appears to be a more specific, and consequently more reliable, measure of thyroid overactivity than the serum cholesterol. Riggs and his co-workers found only 16 of 27 hyperthyroid patients with serum cholesterol values less than the minimum of the normal range, which is about 150 mg per hundred cubic centimeters.[8]

THE BLOOD IODINE IN TOXIC AND IN NONTOXIC GOITER

The clinical groups of thyroid diseases listed in table 1 were collected according to their clinical diagnoses. From this table it may be seen that the average blood iodine concentration is significantly elevated in each form of toxic goiter and that with this increase is associated an elevation of the basal metabolic rate. On the other hand, the average blood iodine in patients with nontoxic goiter does not exceed normal, although it may be accompanied by a moderately increased basal metabolic rate.[9]

TABLE 1.—*The Average Blood Iodine Level in Various Thyroid Diseases, Together with the Standard Error and a Comparison with the Basal Metabolic Rate*

	Blood Iodine, Micrograms per 100 Cc.					
	Method					
	Chromium Trioxide		Dry Ash		Basal Metabolic Rate, %	
Clinical Diagnosis	No. Cases	Mean ± S. E.	No. Cases	Mean ± S. E.	No. Cases	Mean ± S. E.
Normal	39	4.2 ± 0.2	16	11.9 ± 0.8	46	− 5 ± 1
Hypothyroidism	66	3.6 ± 0.1	13	11.8 ± 1.2	77	−16 ± 1 †
Nontoxic diffuse colloid goiter	9	4.4 ± 0.3	5	10.3 ± 2.1	14	− 7 ± 2
Nontoxic nodular goiter	44	3.9 ± 0.2	30	11.5 ± 2.0	72	+ 1 ± 1 †
Toxic nodular goiter	29	7.9 ± 0.8 †	28	15.8 ± 1.1 *	54	+28 ± 2 †
Toxic diffuse colloid goiter	3	6.4 ± 0.7 †	3	18.7 ± 0.8 †	6	+26 ± 9 †
Toxic mixed goiter	4	7.2 ± 1.1 †	..	.....	4	+26 ± 5 †
Exophthalmic goiter	41	9.3 ± 0.6 †	34	17.6 ± 1.0 *	73	+39 ± 3 †
Carcinoma of the thyroid	9	4.8 ± 0.7	3	16.6 ± 2.7 *	11	+16 ± 5 †
Chronic thyroiditis	3	5.2 ± 0.9	..	.....	3	−12 ± 5

* Significantly different from the normal mean; chances are better than 20 to 1 that this difference is not due to chance alone.
† Highly significantly different from the normal mean; chances are better than 100 to 1 that this difference is not due to chance alone.

5. Perkin, H. J., and Hurxthal, L. M.: The Blood Iodine Level Before and After Subtotal Thyroidectomy for Hyperthyroidism, New England J. Med. **215**:698, 1936.

6. Cattell, R. B., and Perkin, H. J.: Recurrent Hyperthyroidism: The Likelihood of Recurrence in Relation to the Preoperative Blood Iodine Level, West. J. Surg. **47**:55, 1939. Perkin, H. J., and Cattell, R. B.: Blood Iodine Levels Related to the Recurrence of Hyperthyroidism, Surg., Gynec. & Obst. **68**:744, 1939. Perkin and Hurxthal.[5]

7. Perkin, H. J.; McFarland, M. D., and Hurxthal, L. M.: Temporarily Induced Thyrotoxicosis from Secretly Ingested Desiccated Thyroid: Its Detection by Blood and Urinary Iodine Estimations, Lahey Clin. Bull. **2**:186, 1941.

8. Riggs, D. S.; Gildea, E. F.; Man, E. B., and Peters, J. P.: Blood Iodine in Patients with Thyroid Disease, J. Clin. Investigation **20**:345, 1941.

9. Curtis, G. M., and Fertman, M. B.: Blood Iodine Studies: VII. The Basal Metabolic Rate and Its Relationship to the Blood Iodine in Thyroid Disease, unpublished data.

Other investigations have likewise revealed the absence of hyperthyroidism in patients with nontoxic goiter. The blood iodine [10] as well as the urinary excretion of iodine [10a,b] is within normal range, while the basal metabolic rate may be normal or even somewhat increased.[10b] Moreover, the iodine balance appears within normal physiologic limits.[11] Perkin and his associates found the average blood iodine level in 111 patients with nontoxic nodular goiter to be identical with that in 112 normal persons.[10c] Turner and his co-workers reported the blood iodine normal in 4 of 5 patients with nontoxic nodular goiter and low in the fifth.[12] Not only the total blood iodine but also the acetone-water-insoluble fraction is diminished, correlated with the varying degrees of exhaustion, atrophy and fibrous replacement shown by microscopic sections of the surgically removed gland.[13] The amount of circulating blood iodine in this disease appears to be dependent on the amount of gland involved in the pathologic changes as well as on the degree of involution or degeneration within the nodules.

Contrasted with this picture of the blood iodine in nontoxic goiter, one finds in any form of toxic goiter a significant increase not only in the average blood iodine but also in the variation of the individual blood iodine values among the different patients. Thus in table 2 the values are arbitrarily divided into five groups, based on normal 1 s.d. and 2 s.d. (one and two times the standard deviation) limits. The per cent of blood iodine values of the combined dry ash and chromium trioxide studies which fall within each of these groups is shown. From this table it becomes clear that the average blood iodine level in toxic nodular goiter and in exophthalmic goiter differs significantly from the normal.

Approximately three quarters of the levels in exophthalmic goiter and nearly that many of the levels in toxic nodular goiter fall above the normal + 1 s.d. limit. Over half the patients with any form of toxic goiter had blood iodine values exceeding the normal + 2 s.d. limit. Of these values 52 per cent were as much as from two to five times the normal mean, whereas the highest value obtained for normal persons did not attain twice the mean.

While there appears to be a difference in the distribution of the blood iodine values in these groups of toxic nodular and exophthalmic goiter above the normal 2 + s.d. limit (table 2), yet it will be seen from table 3 that the blood iodine concentration in toxic nodular goiter can attain as high a level as in exophthalmic goiter. Also, it is to be noted that the average of all the blood iodine values above the normal + 2 s.d. limit for each of these groups is almost identical.

The mean blood iodine level determined by the chromium trioxide technic was 7.9 micrograms per hundred cubic centimeters for 29 patients with toxic nodular goiter and 9.3 micrograms for 41 patients with exophthalmic goiter. By the dry ash method, the corresponding values for 28 patients with toxic nodular goiter and 34 with exophthalmic goiter were 15.8 and 17.6

TABLE 2.—*Distribution of Individual Blood Iodine Values in the Normal* 1 + S.D.* *and* 2 S.D. *Limits*

Normal average blood iodine ±[2] the standard deviation = 4.2 ± 1.2 micrograms per hundred cubic centimeters by the chromium trioxide method [2] and 11.9 ± 3.2 micrograms per hundred cubic centimeters by the dry ash method.[1]

Clinical Diagnosis	Cases, No.	Below −2 S. D., %	−2 S. D. to −1 S. D., %	−1 S. D. to Average, %	Average to +1 S. D., %	+1. S. D. to +2 S. D., %	Above +2 S. D., %
I. Normal	55	0	13	44	24	16	3
II. Nontoxic nodular goiter	74	1	18	42	24	8	7
III. Toxic nodular goiter	57	0	5	11	23	16	45
IV. Exophthalmic goiter	75	0	2	9	11	15	63
V. All toxic goiters, including III, IV, mixed and diffuse colloid	142	1	5	9	16	15	54

* 1 S. D. indicates 1 × the standard deviation; 2 S. D. indicates 2 × the standard deviation, etc.

10. (*a*) Curtis, G. M.; Davis, C. B., and Phillips, F. J.: Significance of the Iodine Content of Human Blood, J. A. M. A. **101**:901 (Sept. 16) 1933. (*b*) Elmer, A. W., and Scheps, M.: The Iodine Content of the Blood and of Urine and the Basal Metabolic Rate: Their Value in the Diagnosis of the Function of the Thyroid Gland, Acta med. Scandinav. **82**:126, 1934. (*c*) Perkin, H. J.; Lahey, F. H., and Cattell, R. B.: Blood Iodine Studies in Relation to Thyroid Disease: Basic Concept of the Relation of Iodine to the Thyroid Gland; Iodine Tolerance Test, New England J. Med. **214**:45, 1936. (*d*) Riggs, Gildea, Man and Peters.[8]

11. Puppel, I. D., and Curtis, G. M.: The Iodine Balance in Nodular Goiter, J. Clin. Investigation **17**: 729, 1938.

12. Turner, K. B.; DeLamater, A., and Province, W. D.: Observations on the Blood Iodine: I. The Blood Iodine in Health, in Thyroid and Cardiorenal Disease and in Leukemia, J. Clin. Investigation **19**:515, 1940.

13. Davison, R. A.; Zollinger, R. W.; Curtis, G. M.; Surington, C. T., and Riley, E. L.: The Fractionation of the Blood Iodine: II, unpublished data.

micrograms, respectively (table 1). Nevertheless, by statistical tests we were unable to prove that these values or those of any two of the groups of toxic goiter included in this study differ significantly from each other; the variation of the blood iodine levels among the individual patients was greater than the difference between the means of each group. In view of the difference between the average basal metabolic rate in toxic nodular goiter and in exophthalmic goiter [9] and in view of an apparent dissimilarity in the iodine balance,[11] some difference in the blood iodine would be expected. This difference might be evidenced quantitatively in the relative proportions of the fractions of blood iodine, if not in the total blood iodine concentrations. With more data it may be possible to demonstrate statistically such quantitative differences. On the other hand, a difference in blood iodine in these two diseases may be more qualitative than quantitative.

Investigators concur that for the most part the blood iodine concentration is elevated in hyperthyroidism.[14] R. G. Turner reported that 10 of 15 patients with this disease had elevated blood iodine values whereas the values of the other third were normal.[14c] Perkin and his coworkers [15] and K. B. Turner [12] have likewise found approximately 30 per cent of their hyperthyroid patients to have a normal blood iodine. Riggs and his associates, however, observed an increased blood iodine in this disease of from two to six times the highest normal level, with no instances of normal values.[16]

Salter and Bassett reported that the plasma protein–bound iodine increases with the degree of thyroid activity while the inorganic ionized iodine in the protein–free plasma filtrate remains relatively constant.[3b] Man, Smirnow and Gildea [3c] observed the total as well as the precipitable serum iodine to be distinctly above the normal range in 15 hyperthyroid patients.

High blood iodine values have also been noted in children with exophthalmic goiter [17] and in patients with induced hyperthyroidism.[10a] The increased blood iodine in exophthalmic goiter rises still higher with administration of iodine, yet the consequent increased storage of iodine in the thyroid gland results ultimately in a diminution of the circulating thyroid hormone.[14b] On initiation of iodine medication to patients with exophthalmic goiter, the inorganic iodine of the blood increases rapidly, yet the organic fraction falls at once,[18] apparently owing to a decrease in thyroid secretion.[19] Bülmann [20] and Man and her associates [3c] report a drop in the plasma protein–bound iodine in hyperthyroidism with iodine medication. On the other hand, there appears to be a relative increase in the organic blood iodine in patients with nontoxic goiter receiving iodine.[21]

TABLE 3.—*Extent of Elevation of the Blood Iodine Levels. Values Above the Normal + 2 S.D.* Limit, Their Average and Maximum*

	Method of Blood Iodine Determination					
	Chromium Trioxide			Dry Ash		
Clinical Diagnosis	Cases, No.	Value, Micrograms per 100 Cc. Average	Highest	Cases, No.	Value, Micrograms per 100 Cc. Average	Highest
Normal.....	1	(7.4)	7.4	1	(19.0)	19.0
Toxic nodular goiter.....	17	10.0	21.5	9	23.1	28.8
Exophthalmic goiter.....	33	10.4	18.4	14	25.2	32.3

* 2 × the normal standard deviation.

14. (*a*) Curtis, G. M., and Davis, C. B.: The Blood Iodine in Diseases of the Thyroid, Proc. Inst. Med. Chicago **8**:14, 1931. (*b*) Curtis, G. M.: The Iodine Relationships of Thyroid Disease, Surg., Gynec. & Obst. **62**:365, 1936. (*c*) Turner, R. G.: Iodine Content of Certain Pathological Bloods in a Goiterous Region, Proc. Soc. Exper. Biol. & Med. **29**:1294, 1932. (*d*) McCullagh, D. R.: Studies in Blood Iodine by the Use of a New Chemical Method, Cleveland Clin. Quart. **2**:15, 1935. (*e*) Man, Smirnow, Gildea and Peters.[3c] (*f*) Riggs, Gildea, Man and Peters.[8] (*g*) Curtis, Davis and Phillips.[10a] (*h*) Elmer and Scheps.[10b] (*i*) Turner, DeLamater and Province.[12]

15. (*a*) Perkin, H. J., and Lahey, F. H.: The Level of Iodine in the Blood, Arch. Int. Med. **65**:882 (May) 1940. (*b*) Perkin, Lahey and Cattell.[10c]

16. Riggs, D. S.; Gildea, E. F., and Man, E. B.: The Clinical Interpretation of Blood Iodine Levels, Connecticut M. J. **5**:209, 1941. Riggs, Gildea, Man and Peters.[8]

17. Curtis, G. M.: Juvenile Thyrotoxicosis, S. Clin. North America **12**:197, 1932. Curtis, Davis and Phillips.[10a]

18. Holst, J.; Lunde, G.; Closs, J., and Pedersen, O. C.: Ueber den inneren Jodstoffwechsel bei primären Thyreotoxikosen (Primär-Basedow), Klin. Wchnschr. **7**:2287, 1928. Holst, J., and Lunde, G.: Intermediate Iodine Metabolism During the Preoperative Treatment of Exophthalmic Goiter, Am. J. Surg. **7**:39, 1929.

19. Lunde, G.; Closs, K., and Pedersen, O. C.: Untersuchungen über den Jodstoffwechsel: III. Untersuchungen über den Blutjodspiegel bei der primären Thyreotoxikose, Biochem. Ztschr. **206**:261, 1929. Sturm, A.: Beiträge zur Kenntnis des Jodstoffwechsels. V. Mitt. Stoffwechselstudien an den überlebenden Schilddrüse: I. Der Jodstoffwechsel der überlebenden künstlich durchströmten Hundeschilddrüse, Ztschr. f. d. ges. exper. Med. **74**:514, 1930.

20. Bülmann, G.: Ueber den Blutjodspiegel: Seine Bestimmung und Seine Beziehung zum Grundumsatz besonders bei Myxoedem und Morbus Basedowi, Skandinav. Arch. f. Physiol., 1938, supp. 12, p. 1.

21. Perkin, H. J., and Hurxthal, L. M.: The Fractionation of the Iodine of the Blood in Thyroid Disease, J. Clin. Investigation **18**:733, 1939.

BLOOD IODINE AND DURATION OF THYROID DISORDER

Perkin and Lahey reported that the blood iodine in hyperthyroidism is correlated with the exhaustion of the patient's store of body iodine when the disease has existed a sufficiently long time.[18a] They found that the blood iodine is usually elevated when the hyperthyroid symptoms have been present for less than nine months.[22] On the other hand, the blood iodine is generally within normal range in patients exhibiting untreated symptoms for one year or more. Further, if the symptoms of clinical hyperthyroidism are allowed to persist untreated for four to five years, the blood iodine level is not only normal but in most cases uninfluenced by thyroidectomy.[22]

Contrary to these observations are those of Riggs and his associates, who could find no relationship between the level of the blood iodine and the duration of symptoms in hyperthyroidism. The average blood iodine of 18 hyperthyroid patients with symptoms present less than one year was 10.5 micrograms pre hundred cubic centimeters, and of 13 with symptoms existing at least one year the average was 10.9 micrograms.[8]

We are unable to find any significant correlation between the blood iodine level and the duration of symptoms in any of the thyroid diseases considered in this report. Nor is there any significant correlation between either the blood iodine or the basal metabolic rate alone and the total duration of either toxic nodular or exophthalmic goiter. On the other hand, we did obtain significant positive multiple correlation coefficients, demonstrating a probable association, between the blood iodine and the combined variables of basal metabolic rate and duration of toxic symptoms in hyperthyroidism or of goiter in nontoxic nodular goiter.[9] However, the association indicates, if anything, that the blood iodine increases, rather than decreases, with an increase in some combination of the other two factors.

BLOOD IODINE IN HYPOTHYROIDISM

In a series of 66 hypothyroid patients whose blood iodine was determined by the chromium trioxide method and in 13 other hypothyroid patients, whose blood iodine was determined by the dry ash method, the average blood iodine values found were 3.6 and 11.8 micrograms per hundred cubic centimeters, respectively. These values do not differ significantly from the corresponding normal values of 4.2 and 11.9 micrograms per hundred cubic centimeters, even though the average basal metabolic rate of these patients is definitely reduced (table 1). While no history of iodine medication was obtained,[23] it is likely that some of these patients had at one time a form of supplementary iodine. Also, possibly contributory to our negative finding may be the occurrence of a somewhat lowered blood iodine of the normal persons living in this goitrous area.

In general, the blood iodine in hypothyroidism as well as in cretinism is admitted to be lower than normal.[24] The blood iodine of cretins has been reported to be 36 per cent [24a] and even decreased as much as 50 or 70 per cent [24b], while the blood iodine in hypothyroidism may be as much as 25 per cent lower than normal.[24c] K. B. Turner and his associates found low and low normal blood iodine levels in 5 patients with hypothyroidism,[12] and R. G. Turner observed normal blood iodine values in 4 patients with this disease.[14c] However, Riggs and his co-workers could find no overlap in the lowered blood iodine of 7 myxedematous patients with that of 26 euthyroid persons.[8] Other investigators have reported that the blood iodine is decreased in hypothyroidism apparently in proportion to the degree of underfunction.[24f] Yet while the decrease in the blood iodine in hypothyroidism ordinarily corresponds to the lowering of the basal metabolic rate, in atypical forms of this disease, Elmer and Scheps reported, the decrease in the blood iodine is not commensurate with the drop in basal metabolic rate.[10b] This may also explain the disproportionately greater reduction of the basal metabolic rate than of the blood iodine which can occur in postoperative myxedema.[24a]

The application of the principle of fractionation of the blood iodine eliminates the incongruous

22. Perkin, H. J., and Lahey, F. H.: Exophthalmic Goiter: Relationship Between the Blood Iodine Level and the Duration of Symptoms in 305 Cases of Exophthalmic Goiter, Arch. Int. Med. **61**:875 (June) 1938.

23. Most of these patients were from the outpatient clinic, and in general their histories did not include any story of possible supplementary iodine.

24. (*a*) Curtis, G. M.; Cole, V. V., and Phillips, F. J.: The Blood Iodine in Thyroid Disease, West. J. Surg. **42**:435, 1934. (*b*) de Quervain, F., and Smith, W. E.: The Iodine Content of Blood in Ordinary Goitres and in Cretinism, Endocrinology **12**:177, 1928. (*c*) Kisch, F.: Zur Klinik atypischer Blutjodwerte, Klin. Wchnschr. **15**:342, 1936. (*d*) Schwenk, W.: Untersuchungen über den Blutjodgehalt im Kindesalter, Monatschr. f. Kinderh. **79**:349, 1939. (*e*) McCullagh, E. P., and McCullagh, D. R.: Clinical Experiences in the Use of Determinations of Blood Iodine, Arch. Int. Med. **57**:1061 (June) 1936. (*f*) de Goés, P., and de Souza Luz, H.: A iodemia nos estados distireoideus, Hospital, Rio de Janeiro **17**:677, 1940. (*g*) Riggs, Gildea, Man and Peters.[8] (*h*) Curtis, Davis and Phillips.[10a] (*i*) Elmer and Scheps.[10b] (*j*) Turner, DeLamater and Province.[12] (*k*) Curtis and Davis.[14a]

picture of a reduced basal metabolic rate coexisting with normal blood iodine in hypothyroidism; this occurs mainly because the portion of the blood iodine containing the iodine of nutrition and of broken-down thyroid hormone is thus separated from the fraction which presumably contains the thyroid hormone or a derivative thereof. The organic blood iodine, whether it is the alcohol-insoluble [21] or the acetone-water-insoluble fraction [25] or the protein-bound plasma iodine,[3a] is consistently low in patients with hypothyroidism.

BLOOD IODINE IN CARCINOMA OF THE THYROID

As will be discussed in a subsequent paper, no significant elevation of the blood iodine was noted in patients with nonthyroid carcinomas, a group which did not include any patients with malignant neoplasms of the liver.[26] However, the blood iodine in carcinoma of the thyroid may occasionally be elevated. Such an elevation previously reported [27] was found in 3 patients, whose blood iodine was determined by the dry ash method (table 1). Two of the patients had both an increased blood iodine and an increased basal metabolic rate; in the third, a woman with goiter of forty years' duration, only the basal metabolic rate was elevated.

TABLE 4.—*Comparison of Ranges and Averages of Blood Iodine Levels (Chromium Trioxide Method)*

Clinical Diagnosis	No. of Cases	Range, Micrograms per 100 Cc.	Average, Micrograms per 100 Cc.
Normal	39	2.3 - 7.4	4.2
Carcinoma of the thyroid	9	2.2 - 7.8	4.8
Toxic nodular goiter	29	3.2 -21.5	7.9 *
Exophthalmic goiter	41	3.6 -18.4	9.3 *

* Highly significantly greater than normal.

On the other hand, while the average basal metabolic rate was likewise significantly increased in 9 other patients with thyroid carcinoma, whose blood iodine was determined later by the chromium trioxide technic, the average blood iodine concentration found was 4.8 micrograms per hundred cubic centimeters, which does not differ significantly from the normal average of 4.2 micrograms (tables 1 and 4). Normal blood iodine values were observed in patients who had had goiter over ten and twenty and for thirty years; yet the highest value, 7.8 micrograms per hundred cubic centimeters, was found in a patient whose goiter was also present for "many" years. A low normal blood iodine of 2.5 micrograms per hundred cubic centimeters was noteworthy in a patient with carcinoma occurring in an aberrant lateral thyroid.

In 3 other isolated determinations of the blood iodine in cases of carcinoma of the thyroid reported in the literature, the level of the blood iodine was found to be normal.[28] The basal metabolic rate observed in 2 of the cases was, as we have also noted in our series, elevated.[24e]

It would consequently appear that the level of the blood iodine in carcinoma of the thyroid is more dependent on the nature of the thyroid gland in which the malignant growth arises than on the malignant growth itself. As we have mentioned, the average blood iodine in nontoxic goiter is also normal, even in the presence of an elevated basal metabolic rate. This is apparently likewise true in various forms of carcinoma.[26] Further, we were unable to find any correlation between the blood iodine and either the duration of the symptoms due to the carcinoma or the duration of a preceding goiter, when such was reported. Thus, we are unable to present any evidence of an association between the height of the blood iodine and the amount of degeneration taking place within the goiter. More data may, however, reveal such a correlation, and pathologic studies may indicate that the degree of degeneration, dependent on or possibly even independent of the time factor, may play an important role.

BLOOD IODINE IN THYROIDITIS

In 3 patients with chronic thyroiditis the average blood iodine determined by the chromium trioxide method was 5.2 micrograms per hundred cubic centimeters but was not significantly elevated. The values ranged from 3.4 to 6.4 micrograms per hundred cubic centimeters. On the other hand, K. B. Turner and his co-workers reported elevated blood iodine values in 2 patients with thyroiditis.[12] Riggs and his associates found a similarly high level of blood iodine in 1 patient with thyroiditis; there were no other symptoms or physical findings of hyperthyroidism.[8]

SUMMARY

1. Analyses of blood iodine in conjunction with the determination of the basal metabolic rate

25. Davison, R. A.; Zollinger, R. W., and Curtis, G. M.: The Fractionation of the Blood Iodine: I. Findings in Patients with Normal Thyroid Function and with Hypothyroidism, J. Lab. & Clin. Med. **27**:643, 1942.

26. Curtis, G. M., and Fertman, M. B.: Blood Iodine Studies: VIII. The Blood Iodine in Non-Thyroid Disease; IX. The Basal Metabolic Rate and Its Relationship to the Blood Iodine in Non-Thyroid Disease, unpublished data.

27. Curtis.[14b] Curtis, Cole and Phillips.[24a]

28. Turner, DeLamater and Province.[12] McCullagh and McCullagh.[24e]

are of importance in the differential diagnosis of thyroid dysfunction.

2. The average blood iodine level was found to be significantly elevated in all forms of toxic goiter, and variations in the individual blood iodine values were likewise found to exceed those of normal persons. Associated with the increase in the blood iodine there occurred an elevated average basal metabolic rate.

In no two groups of toxic goiter, including the exophthalmic variety, was there found by statistical test any significant difference between the average blood iodine concentrations. However, some difference in the nature or quantity of the whole or fractionated blood iodine might be expected in exophthalmic goiter and should be further investigated.

It was noted that the blood iodine may rise as high in toxic nodular goiter as in exophthalmic goiter.

3. On the other hand, the average blood iodine level was not significantly elevated in nontoxic nodular goiter and in nontoxic diffuse colloid goiter. The average basal metabolic rate was significantly increased in nontoxic nodular goiter but averaged only —7 per cent in diffuse nontoxic colloid goiter.

4. The average blood iodine in 79 patients with hypothyroidism was not significantly lower than that in normal persons from this goitrous region, although the average basal metabolic rate was definitely reduced. The value of the average blood iodine may have been influenced by previous iodine medication in certain instances, of which, however, there was no record. The importance of fractionation of the blood iodine, especially for such patients, is emphasized.

5. The average blood iodine in 9 patients with carcinoma of the thyroid, unlike that of a previous group of 3 similar patients, did not differ significantly from the normal, in spite of an elevated basal metabolic rate. There was no significant correlation between the blood iodine level and the duration of the symptoms due to the carcinoma or to those of goiter when such was recorded. It would appear that the level of the blood iodine in carcinoma of the thyroid is more dependent on the nature of the thyroid gland in which the malignant growth occurs than on the malignant growth itself.

6. In none of the thyroid disorders investigated was there found any significant linear correlation between the level of the blood iodine and the duration of symptoms or of goiter. However, that some association may exist was indicated by a significant positive multiple correlation coefficient of the blood iodine in relation to the basal metabolic rate and the duration of toxic symptoms in hyperthyroidism or of goiter in nontoxic nodular goiter. If anything, this relationship shows that the blood iodine increases rather than decreases with some combination of the other two factors.

7. In 3 patients with chronic thyroiditis, the average blood iodine was not significantly elevated.

EARLY AND LATE POSTOPERATIVE AMBULATION

A COMPARATIVE STUDY OF THREE HUNDRED AND THREE CASES

VINCENTE D'INGIANNI, M.D.

NEW ORLEANS

The exponents of early postoperative ambulation are becoming progressively more numerous, if one is to judge by the number of cases reported by individual authors. Zava [1] alone reported 6,000 cases. The literature surveyed in the course of this study presented no instance of reversion to the older modes of treatment once early ambulation had been tried.

Although propaganda for early ambulation has been under way, several writers have claimed to have "discovered" or "hit on" this manner of postoperative treatment independently. Zava noted that insane patients moved about frequently immediately after operation with no ill effects. Nelson [2] observed that children did well in spite of the fact that they were restless and active and that animals walked immediately after surgical treatment with no disruption of the wound. Leithauser [3] and Nelson [2] independently observed that self ambulation not only caused no ill effects in children but resulted in benefit.

My own experience with this mode of treatment dates from the hospitalization of an 82 year old woman who had a cholecystectomy. Being especially anxious to prevent pneumonia, I instructed the nurses to have the patient sit in a wheel chair. This was accomplished after she took a few steps. Only some time later was it realized that the patient sat up on the second postoperative day. The results were good, and the evidence for and against early ambulation was examined. The objections appeared to be nonphysiologic and empiric.

If persons are not to become ambulatory within the first day or two, why allow them to get up on the tenth day, when the sutures are weakest? If muscles are to be maintained in normal tone, why splint them? If circulation is increased by muscular contraction, why slow it down by immobilization? If stasis promotes clotting, which predisposes to pulmonary embolism, why immobilize the patient? If early ambulation promotes healing, why not practice it?

With these thoughts in mind, I allowed all my patients to be out of bed immediately after operation, as early as the first day. In order to determine better the advantages and the disadvantages of this so-called radical change in postoperative treatment, a comparative study was made of 303 patients who were treated during the same period, 150 of whom received relatively conservative treatment and 153 of whom became ambulatory immediately after operation. This study was made possible through the cooperation of Dr. Christopher Bellone and Dr. Nicholas Tessitore.

Some facts which suggest that patients should be made ambulatory soon after operation are as follows:

1. Healing of wounds has become a lively topic of discussion and is closely associated with early ambulation. It has been shown that dogs and rats which are allowed to be active soon after operation show an observable and a recordable difference in the tensile strength of the operative wound, as compared with animals which are permitted progressive increase in exercise from day to day. The wounds of animals which move about early after operation not only show an increase in tensile strength but are less likely to rupture after the fifth day. Zava demonstrated that early rising promotes cicatrization.

2. Many experimenters have shown that disruption of wounds occurs from the fifth to the ninth day; and clinicians have cited the eighth to the fourteenth day after operation as the period in which this complication is most likely to occur. Yet the usual method of treatment has been to allow the patient to rise and move about during this particular phase of healing, when a wound closed with surgical gut is weakest.

3. Pulmonary emboli may occur between the third and the thirteenth postoperative day. This period again coincides with the usual time of ambulation and accounts for the sudden deaths

1. Zava, L.: The Advantages of Early Rising After Operations, Policlinico (sez. prat.) **47**:865, 1940.

2. Nelson, H.: Early Ambulation Following Section of the Anterior Abdominal Wall, Arch. Surg. **49**:1 (July) 1944.

3. Leithauser, D. J.: Confinement to Bed for Only Twenty-Four Hours After Operation, Arch. Surg. **47**: 203 (Aug.) 1943. Leithauser, D. J., and Bergo, H. L.: Early Rising and Ambulatory Activity After Operation, ibid. **42**:1086 (June) 1941.

which occur when the patient sits up for the first time, causing the thrombus, which was formed about seven days before, to break off. Ambulation, if not allowed immediately after operation, should be delayed until the thrombus has been well organized. Potts and Smith [4] showed that muscular contraction of the lower extremities of the dog stimulated circulation, with an increase of 250 per cent in the volume flow of blood in the inferior vena cava. Thus, with a quickened flow, little time is permitted for clotting, and any elements for clotting accumulated during the first day are swept away by the increased flow. Zava did not report any instance of pulmonary embolus in his 6,000 cases.

4. Pneumonitis, particularly hypostatic pneumonia in the aged, is a constant bugbear to the surgeon. Nanta [4a] pointed out that the effect of gravity is an important factor to be overcome, for it tends to produce stasis, followed by edema of the tissues, which, in turn, encourages the growth of organisms. The circulation time is increased from one and five-tenths to four and five-tenths seconds by a change from the sitting to the standing position. Constant massage of the vascular system by the contracting muscles accelerates the flow of blood. Each muscle is a "heart" and acts like a substation in sending on the flow of blood. Realizing, further, that anesthesia predisposes to infection of the respiratory tract and phlebitis, one does well to avoid the additional complication of stasis.

Beecher [5] pointed out that the volume of tidal air is greatly diminished in patients who have had a laparotomy and that rapid, shallow breathing is also a factor in diminution of the tidal air. Churchill and McNeil [6] stated that the vital capacity is decreased 30 per cent when tight dressings are applied to the upper part of the abdomen. It is necessary to apply dressings loosely and avoid splinting of the abdominal muscles, which are greatly depended on for respiration. Moersch [6a] noted that the lower the vital capacity becomes and the closer it approaches the volume of tidal air, the greater the operative risk. Powers [7] stated the belief that in all surgical cases preoperative determination of vital capacity should be made to ascertain the suitability of the patient for operation.

Lyford [7a] found that the incidence of infection of the respiratory tract after anesthesia in cases in which there was no infection prior to operation was as follows: after anesthesia induced with ether, 5.8 per cent; after anesthesia induced with cyclopropane, 4.9 per cent, and after spinal anesthesia, 7.5 per cent. In cases in which there was a chronic infection or some type of infection of the respiratory tract thought not to be a contraindication to surgical intervention, further complicated infection of the respiratory tract occurred in 13.5 per cent of the cases after administration of ether, in 17.5 per cent after administration of cyclopropane and in 39.5 per cent after spinal induction anesthesia. Cutler [8] wrote that in 4 per cent of cases in which operation on the lower portion of the abdomen and in 8 per cent of cases in which operation on the upper portion of the abdomen was performed pulmonary complications developed. Regardless of personal opinions of such statistics, it is evident that anesthesia predisposes to infection of the respiratory tract, particularly in the presence of stasis in the vascular system and retarded circulation. Every effort to avoid the pathophysical phenomena imposed by anesthesia and the reclining position should therefore be made.

Metabolism is greatly slowed down by inactivity. Early ambulation causes an early return to normal vital capacity. The standing position relieves subdiaphragmatic pressure and thus permits greater expansion of the lungs. Leithauser [8] expressed the opinion that return to normal vital capacity parallels convalescence.

5. The power of suggestion, or the psychologic approach, in hastening recovery is not entirely without foundation. When a patient who has had a serious operation can sit up, eat well, and walk just like a "whole" person, surely a mental victory too has been achieved. The patient requires less nursing and attention and is on his way back to a useful existence.

Recently a girl who had had a laparotomy was up and about on the fourth postoperative day acting as a nurse for her roommate. She was completely rehabilitated and happy in her achievement. Thus, with early ambulation the morbidity rate is cut down and the patient is enabled to return to work much earlier. The usual long

4. Potts, W. J., and Smith, S.: Pulmonary Embolism, Arch. Surg. **42**:661 (April) 1941.

4a. Pinoy, A., and Nanta, A.: Sclérose et endothéliose mycosiques, Strasbourg-méd. (pt. 2) **86**:141, 1928.

5. Beecher, H. K.: Measured Effect of Laparotomy on Respiration, J. Clin. Investigation **12**:639, 1933.

6. Churchill, E. D., and McNeil, D.: The Reduction in Vital Capacity Following Operation, Surg., Gynec. & Obst. **44**:483, 1927.

6a. Moersch, H. J.: The Vital Capacities of 1,000 Surgical Patients, Arch. Int. Med. **37**:128 (Jan.) 1926.

7. Powers, J. H.: Vital Capacity: Its Significance in Relation to Postoperative Pulmonary Complications, Arch. Surg. **17**:304 (Aug.) 1928.

7a. Lyford, J., III: Postoperative Infection of the Respiratory Tract in Relationship to Inhalation and Spinal Anesthesia, Arch. Surg. **44**:35 (Jan.) 1942.

8. Cutler, E. C., and Hoerr, S. O.: Postoperative Pulmonary Complications, Proc. Interst. Postgrad. M. A. North America (1941), 1942, p. 232.

period of rest in bed and inactivity, which is dreaded by any purposeful person, is appreciably curtailed. The cost of hospitalization and convalescence is reduced as much as $75 to $250, an important factor to the ordinary working man.

In preparation for this so-called radical postoperative treatment, the patient is instructed on the day prior to the operation as to what is expected of him. He is told that early ambulation is an aid in getting well and in preventing pulmonary conditions, which often complicate surgical treatment. He is told that during the first three days cooperation will not be easy; that he will wish to be left alone; that he will feel bad but that if he does cooperate, he will be well enough on the fourth day to walk and go home. This usually gives the patient enough strength to bear the discomfort. On the first postoperative day he is to sit up on the side of the bed; on the second day he is to move freely along the side of the bed or to sit in a chair; on the third day he is to sit in a chair and possibly to walk, as he usually does. Some patients complain bitterly; a few even faint, but by the second day most of the discomfort passes. It is interesting to note the determination to move about, even in persons who fail in their first attempt. They are ready the next day to try again. A patient who had a hernioplasty and was made ambulatory early after operation complained a great deal; however, a year later, when he was operated on for another hernia, he got up and walked on the first day without complaints or without being told to do so. In instructing the patient as to how much walking he should attempt, I tell him that he can move about as much as he desires until he has a sense of approaching fatigue. Some persons are able to return to work in two weeks, while others linger. The patient who does not wish to become ambulatory early is allowed to remain in bed as long as he desires. However, if he shares a room with another patient who moves about and goes home soon after operation, he, too, usually decides to try ambulation. No patient has stated that he has regretted early ambulation.

The two most frequently mentioned contraindications are pulmonary emboli and the danger resulting from closure of the wound with absorbable material. The incidence of pulmonary emboli in cases of early ambulation is certainly not greater, and is demonstrated by many to be far less, than in cases in which the patient is kept quiet. To date there have been reported but 5 cases of pulmonary embolism among the 20,000 cases in which the patient became ambulatory early, or 0.025 per cent. Since in many of the 20,000 cases surgical gut was used for closure with no reported ill effects, there seems little to be feared on that score.

Early ambulation made possible a saving of at least $1,464 in hospital expenses for the patients in the present series. If the compound earnings yielded by an early return to work are added to this figure, the sum total should be startling. A shortened period of hospitalization also permitted a quick turnover of patients.

TABLE 1.—*Age Distribution*

Years	Early Ambulation		Rest in Bed	
	Females	Males	Females	Males
0-15	6	6	5	3
16-30	74	9	98	3
31-45	22	9	26	1
46-60	12	3	10	1
61-75	1	1	3	0
Total	125	28	142	8

The present comparative study was carried out on 150 patients who were treated after operation with relatively long periods of rest in bed and 153 patients who were treated by early ambulation. The age distributions in the two groups and the number in each age decade were similar (table 1).

The patients were further divided into three groups, as follows: (1) patients having appendectomy alone; (2) patients having a surgical operation on the lower portion of the abdomen, with or without appendectomy or with or without vaginal repair, and (3) patients having cholecystectomy.

TABLE 2.—*Data on Patients After Appendectomy (Average Values)*

	Early Ambulation		Rest in Bed	
	Females	Males	Females	Males
Number of days in hospital	4.8	3.1	7.2	5.1
Age	19.2	17.6	23.8	15.5
Increase in temperature (degrees F.)	1.2	1.3	1.6	1.0
Number of days fever persisted	2.0	1.4	3.5	1.2
Number of complications	0.0	1.0	3.0	0.0
Postoperative day diet was ordered	2.0	2.0	5.0	3.0
Number of hypodermic injections of a narcotic	2.2	3.5	6.5	5.0
Number of catheterizations	0.0	0.0	2.0	1.6
Number of patients discharged with fever	0.0	1.0	7.0	0.0
Number of patients with chromic surgical gut sutures	9.0	15.0	28.0	5.0
Number of patients with cotton sutures	14.0	5.0	0.0	0.0

Table 2 demonstrates significant differences between the ambulatory and the bed patients. The female patients having appendectomy alone who were treated by rest in bed remained in the

hospital two and four-tenths days longer on the average than those who were treated by early ambulation. One ambulatory patient and 5 bed patients had a temperature over 2 degrees (F.) above normal. The duration of fever was slightly longer for the bed patients. Food was tolerated on the first or second day by patients who became ambulatory early, whereas it was not given until the third to the fifth day to those who remained in bed. The average number of injections

TABLE 3.—*Data on Patients After Laparotomy (Average Values)*

	Early Ambulation		Rest in Bed	
	Females	Males	Females	Males
Number of days in hospital	6.9	7.8	9.9	7.3
Age	29.1	53.0	29.4	24.5
Increase in temperature (degrees F.)	1.6	1.2	3.9	3.9
Number of days fever persisted	4.0	3.8	9.8	5.3
Number of patients with complications	7.3	17.1	30.0	0.0
Postoperative day diet was ordered	2.4	2.2	5.0	3.2
Number of hypodermic injections of a narcotic	6.2	5.7	9.1	5.8
Number of catheterizations	0.5	0.0	2.9	3.6
Number of patients discharged with fever	9.0	0.0	11.0	2.0
Number of patients with chromic surgical gut sutures	34.0	1.0	103.0	8.0
Number of patients with cotton sutures	62.0	6.0	0.0	0.0

of morphine sulfate, dihydromorphinone hydrochloride or codeine sulfate administered to the bed patients was five to six and five-tenths, whereas the average number administered to the ambulatory patients was two and eight-tenths to three and seven-tenths. The fact that the ambulatory patients required fewer injections of a narcotic indicates that they overcame discomfort more rapidly. It also partially accounts for their spontaneous bowel movements and their infrequent need of purgation, since it is believed that rest in bed and drugs, such as morphine and dihydromorphinone, tend to produce constipation. Catheterization was not necessary for a single ambulatory patient, but was usually required once or twice by each bed patient. Seventeen per cent of the bed patients and 9 per cent of the ambulatory patients were discharged from the hospital with fever. The wounds of all bed patients were closed with chromic surgical gut, as were 62 per cent of the wounds of patients who walked early; the rest were closed with cotton.

The term "laparotomy" (table 3) included hernioplasty alone or in combination with appendectomy. After this operation the period of hospitalization was three days less for patients who became ambulatory early than for those who remained in bed. The increase in temperature varied from 1.2 to 1.6 degrees (F.) for ambulatory patients and averaged 3.9 degrees (F.) for bed patients. The duration of elevation of temperature was from three and eight-tenths to four days for ambulatory patients and from five and three-tenths to nine and eight-tenths days for the bed patients. Twenty-four ambulatory patients had complications, as compared with 30 bed patients. Complications included any pathologic condition of the respiratory or the circulatory apparatus or of the extremities. Nine of the ambulatory patients and 13 of the bed patients were discharged from the hospital with fever. Catheterization was not necessary among the male patients who practiced early rising and was done on an average of 0.5 time among the female ambulatory patients; on the other hand, the male bed patients were catheterized 3.6 times and the female bed patients 2.9 times. The wounds of all the bed patients were closed with surgical gut; the wounds of 68 patients with early ambulation were closed with cotton.

Vomiting on the second day occurred in 4 per cent of the patients who became ambulatory early after operation, as against 32 per cent of the patients who remained in bed. Postoperative purgatives were needed by only 10 per cent of the patients who rose early, whereas purgatives were ordered for 85 per cent of the bed patients. Furthermore, the ambulatory patients were not given enemas before operation, whereas all the

TABLE 4.—*Data on Patients After Cholecystectomy (Average Values)*

	Early Ambulation	Rest in Bed
Number of days in hospital	7.1	13.1
Age	46.1	48.0
Increase in temperature (degrees F.)	2.1	3.6
Number of days fever persisted	3.7	6.7
Number of complications	2.0	3.0
Postoperative day diet was ordered	2.2	7.0
Number of hypodermic injections of a narcotic	7.0	13.0
Number of catheterizations	0.0	5.0
Number of patients discharged with fever	0.0	1.0
Number of patients with chromic surgical gut sutures	2.0	6.0
Number of patients with cotton sutures	7.0	0.0
Number who died	1.0	1.0

bed patients, except those in emergency cases, were given enemas.

With regard to the patients who had cholecystectomy, table 4 indicates that those who were made ambulatory early required less hospitalization and fewer injections and that the elevation of temperature was less than for the patients who remained in bed.

Up to this point the purpose of this study has been to bring to light the advantages of early am-

bulation, to shatter doubt as to its danger, to demonstrate its practicability and to reveal its popularity and widespread acceptance. However, early ambulation should not be considered a cure-all for every postoperative problem. Some writers have given the impression that there can be no complications when early ambulation is practiced. This, however, is not true, as evidenced by the results in the 153 patients studied here. Postoperative complications, such as pulmonary emboli, pyelocystitis, thrombophlebitis and pneumonia, have occurred with early ambulation, despite the claims of some supporters of this method of postoperative treatment. I handled the following cases personally; in each instance early ambulation was practiced, yet unexpected complications developed, which one would conclude were highly improbable after reading the literature on early ambulation.

REPORT OF CASES

CASE 1.—When Mrs. J. was seven months pregnant, she had acute appendicitis. With the use of general anesthesia, an appendectomy was done. The patient was allowed to walk on the second day and was doing well. She was afebrile until the sixth day, when her temperature rose to 104 F. She aborted, and pulmonary emboli developed; her condition improved, but she suddenly died.

CASE 2.—Mrs. T. had an appendectomy, after which she did well until the sixth day, when her temperature rose to 102 F. Edema and pain developed in the lower left extremity; the diagnosis was superficial thrombophlebitis.

CASE 3.—Mrs. S. had a cholecystectomy and became ambulatory on the second day. On the fifth day her temperature was 102 F., with accompanying pain in the lower right extremity. The diagnosis was thrombophlebitis.

CASE 4.—Mr. M. had a cholecystectomy and was permitted to sit up in bed on the first day and in a chair on the second day. A cough and then lobar pneumonia developed. Herniation of the viscera occurred on the ninth day. The operative wound had been closed with cotton sutures.

CASE 5.—Mrs. D. had a panhysterectomy and was walking about, when severe pyelocystitis developed.

CASE 6.—Mrs. L. had a cesarean section and was up in a chair and feeling well, when, on the fourth day, pain and edema of the right lower extremity developed; the superficial veins were tender, red and painful to touch. Her temperature rose to 103 F. The diagnosis was thrombophlebitis.

CASE 7.—Master S., a 6 year old boy, had an appendectomy and was up and walking on the second day. His abdomen became greatly distended, and he began to vomit. The diagnosis was acute gastric dilatation.

In these few cases complications were observed which many of the supporters of early ambulation claimed have been eliminated. Early ambulation did not prevent phlebitis in a patient who had walked on the first and second postoperative days. Sitting up did not prevent pneumonia in a patient who was up in a chair one day prior to the rise in temperature and the onset of chill, followed closely by lobar pneumonia.

SUMMARY

This comparative study of 303 patients indicates several distinct advantages of early ambulation as a method of postoperative treatment. The periods of hospitalization and convalescence are shortened; thus, the patient's expense is curtailed and the hospital can accommodate an additional patient in his stead. The patient regains his health, returns to work much earlier and thus recovers his useful activity and earning power again. A mental attitude of well-being is maintained, and there is no long period of abnormal body function, with a special diet, rest in bed, catheterization and purgation.

Early ambulation does not increase the frequency of complications or endanger the person, as case reports and experience prove. However, neither does early ambulation eliminate all the complications as many advocates of this postoperative treatment have claimed.

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TOPICAL USE OF CONCENTRATED PENICILLIN IN SURFACE-ACTIVE SOLUTION

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At two meetings [1] held recently to discuss the end results of penicillin therapy, surgeons from two of the largest government hospitals for treatment of wounds of the extremities presented opinions serving to qualify prevailing optimism about the value of this agent. Although widespread use of penicillin has proved generally successful, both prophylactically and in the control of wound sepsis, there remain examples of indifferent success or outright failure which in our opinion may be based partly on inadequate technic.

Florey and Jennings [2] have described the principal causes of failure in the use of penicillin as follows: Dead tissue, slough or sequestrum is the focus of infection; an infected area is not being reached by the drug; the dose is too small or application too infrequent; bacteria are not sensitive and penicillin is no longer potent. Assuming that a potent preparation is used on penicillin-susceptible organisms, the problem becomes simply one of reaching the pathogens with a bacteriostatic level of penicillin and maintaining it for a sufficient period to be therapeutically effective. When topical application is made, present methods call for a maximum concentration of 500 units of penicillin per cubic centimeter of isotonic solution of sodium chloride.[3] The statements of Florey and Jennings [2] make it appear that a higher concentration may be required.

It is now evident that the undesirable reactions of penicillin reported by earlier workers were attributable in the main to toxic impurities and not to the active penicillin fraction.[4] Increased pharmacologic purity renders the maximum limit of 500 units per centimeter unduly conservative, and higher concentrations are coming into limited use.[5] The tendency to use more concentrated and massive doses of penicillin would be accelerated if clinicians were generally aware of the recent findings of Demerec [6] on the mode of origin of penicillin-resistant strains of Staphylococcus aureus. He showed that resistance to penicillin is not induced but arises spontaneously by mutation, and he demonstrated a few naturally resistant organisms in every mass inoculum of the standard susceptible strain. At a level of 0.15 Oxford unit per cubic centimeter all bacteria, including the resistant members, were killed. However, at a concentration of 0.064 Oxford unit per cubic centimeter the few resistant individuals survived, forming the progenitors of subsequent generations, all of which were now resistant by heredity. By mutation and continued selection, bacteria resistant to 250 units per cubic centimeter were obtained. What is probably the clinical counterpart of such a process of artificial selection has been reported by Florey and Florey.[7] Natural defense mechanisms of the body may be able to cope with a small number of resistant organisms, but their selection by topical application of low doses of penicillin must be recognized as a definite hazard.

From the Grace Clinic, Brooklyn, and the Biological Laboratory, Cold Spring Harbor, N. Y.

1. Carpenter, G. K.: The Morbidity of Compound Fractures and the Value of Penicillin Therapy, read before the Brooklyn Surgical Society, Nov. 2, 1944 and Jan. 4, 1945. Fett, H. C., in discussion on Carpenter. Meleney, F. L.: Antibiotic Therapy in Surgical Infections, read before the Brooklyn Surgical Society, Nov. 2, 1944 and Jan. 4, 1945.

2. Florey, H. W., and Jennings, M. A.: The Principles of Penicillin Treatment, Brit. J. Surg. (supp.) **32**:112 (July) 1944.

3. Keefer, C. S.; Blake, F. G.; Marshall, E. K., Jr.; Lockwood, J. S., and Wood, W. B., Jr.: Penicillin in the Treatment of Infections: A Report of Five Hundred Cases, J. A. M. A. **122**:1217 (Aug. 28) 1943.

4. Lyons, C.: Penicillin Therapy of Surgical Infections in the U. S. Army, J. A. M. A. **123**:1007 (Dec. 18) 1943.

5. Harford, C. G.; Martin, S. D.; Hagerman, P. O., and Wood, W. B., Jr.: Treatment of Staphylococcic, Pneumococcic, Gonococcic and Other Infections, J. A. M. A. **127**:253 (Feb. 3) 1945.

6. Demerec, M.: Production of Staphylococcus Strains Resistant to Various Concentrations of Penicillin, Proc. Nat. Acad. Sc. **31**:16 (Jan.) 1945.

7. Florey, M. E., and Florey, H. W.: General and Local Administration of Penicillin, Lancet **1**:387 (March 27) 1943.

Other reasons exist for a revaluation of dosage and concentration. Except in certain limited regions, whenever penicillin is applied locally much of it is rapidly lost through diffusion away from the site of application. Since loss is a function of time, it follows that an initial high concentration of penicillin is more likely to assure bacteriostatic activity during the not inconsiderable period required for effective inhibition. In addition, both diffusion and dilution will reduce the concentration of penicillin in tissues or cavities immediately adjacent to the main focus of infection. Since these neighboring areas may in themselves be infected, it becomes important to have a concentration level not always realizable systemically and sufficient to be bacteriostatic in the presence of diluting fluids and in areas contiguous to the application site. When penicillin is injected into the pleural cavity, the diluting influence of any existing empyema must be considerable.

This principle of therapy has been further emphasized by the work of Struble and Bellows,[8] who make the following statement: "When penicillin can be applied topically, an enormous concentration can be achieved locally, which surpasses by far any value which can be secured even by the most massive intravenous doses." By using on dogs a dosage of penicillin one hundred times greater than that commonly given to human beings (12,800 units per kilogram of body weight in highly concentrated form—20,000 units per cubic centimeter of solution), they demonstrated that none was recovered in the bone marrow up to three hours following injection. The dogs used were full grown, and histologically the bone structure would resemble that of human adults. We do not feel that the significance of this fact has been fully appreciated by clinicians dealing with compound fractures and with acute and with chronic osteomyelitis.

It is true that acute hematogenous osteomyelitis of the fulminating type with septicemia and multiple abscess formation calls for systemic treatment. On the other hand, chronic local osteomyelitis of long standing may be treated locally, provided all possible extrinsic sources of infection are ruled out. Any improvement noted in chronic osteomyelitis must be regarded as temporary until proved to be otherwise. In the meantime, Dickson's[9] remarks on the role of "quiescent foci" in the recurrence of acute symptoms suggest that local use of penicillin combined when necessary with judicious surgical measures may be of value. A decision to use penicillin locally or systemically often depends on the factor of accessibility and extent of the infection. Jeffrey[10] observed that penicillin may fail, even against susceptible organisms "in necrotic soft tissue and necrotic bone and in the center of abscesses and masses of fibrinopurulent material." The local use of high concentrations of penicillin in a solution known to be an effective solvent of sputum and empyema fluid might aid in effectively neutralizing these isolated avascular regions that serve as a potential source of future infection. Therefore we have employed 4,000 units of penicillin per cubic centimeter in isotonic solution of sodium chloride with 0.1 per cent of the wetting agent sodium tetradecyl sulfate, or Tergitol (sodium 2-methyl-7-ethylundecyl-4 sulfate),[11] for topical application.

The place of detergents in medicine has been discussed in a recent editorial.[12] Sodium tetradecyl sulfate has previously been used in surgical procedures,[13] and its combination with penicillin is predicated mainly on the properties of wetting activity, including dispersal power and solvent action. But since penicillin is not effective against many bacterial invaders that may be present in the usual type of mixed infection, i. e., organisms of the coliform and subtilis-mesentericus groups, the use of a nonspecific germicide, such as sodium tetradecyl sulfate, becomes desirable as a general bacteriocidal agent, quite aside from its wetting properties. This is especially true when one of the organisms present in a mixed infection is capable of producing a penicillin-inactivating enzyme, such as penicillinase. Certain other wetting agents have been found to be compatible with penicillin,[14] and we have tested the penicillin–sodium tetradecyl sulfate solution in vitro, finding it fully potent. It is important to note that at a concentration of 4,000 units of penicillin per cubic centimeter many species of bacteria not ordinarily considered susceptible to penicillin might be effectively inhibited, even in the absence

8. Struble, G. C., and Bellows, J. O.: Studies on the Distribution of Penicillin in the Eye and Its Clinical Application, J. A. M. A. **125**:10 (July 8) 1944.

9. Dickson, F. D.: The Clinical Diagnosis, Prognosis and Treatment of Acute Hematogenous Osteomyelitis, J. A. M. A. **127**:212 (Jan. 27) 1945.

10. Jeffrey, J. S.: Application of Penicillin to War Wounds, Brit. J. Surg. (supp.) **32**:124 (July) 1944.

11. The Tergitol used in this work was supplied by Wallace & Tiernan Products, Inc., Belleville, N. J.

12. Medical Use of Detergents, editorial, J. A. M. A. **126**:1152 (Dec. 30) 1944.

13. Brantigan, O. C., and Owens, J. C.: Sodium Tetradecyl Sulfate Used in the Treatment of Acute Pyogenic Empyema of the Pleural Cavity, Bull. School Med., Univ. Maryland **26**:247 (April) 1942.

14. Herrill, W. E., and Heilman, D.: Tissue Culture Studies on Cytoloxicity of Bactericidal Agents: Cytotoxic and Antibacterial Activity of Gramicidin and Penicillin; Comparison with Other Germicides, Am. J. M. Sc. **206**:221 (Aug.) 1943.

of a detergent. Except in a minority of wound pathogens, resistance to penicillin is relative, not absolute.

It is admittedly difficult to evaluate the variables involved when penicillin is applied in a more concentrated form and simultaneously in a solution with surface activity. Yet military failures in chemotherapy, such as those reported by Furlong and Clark [15] in the treatment of open fractures of the femur, may to some extent be preventable. Chemotherapy is certainly not a substitute for surgical repair. But if penicillin is to be used, the conclusions made by Florey and Jennings [2] are highly significant. In their light a therapeutic use for topically applied, concentrated, surface-active solutions of penicillin appears to be virtually self evident. In agreement with this fundamental approach we are reporting our brief experience.

Case 1.—A 68 year old man, who was first seen by us Feb. 24, 1944, had received a compound fracture of the middle third of the left tibia and fibula nine years previously. Thereafter he had had almost constant drainage from two sinuses over the fracture site. Results of routine laboratory studies were essentially normal; all points of focal infection had been eliminated. A culture made from material from the draining sinus was reported as yielding growth of Staph. aureus, extremely hemolytic and strongly pigmented. The culture was tested for susceptibility to penicillin, the technic of Demerec being used. In this case of chronic osteomyelitis, the highly toxic strain of Staphylococcus was not resistant to penicillin.

On August 14 he was hospitalized and received a dose of 400,000 units of penicillin, 10,000 units being injected into the sinus and 5,000 into the second sinus and the remainder given intramuscularly in doses of 10,000 units every three hours. He was discharged on August 18 and appeared improved. However, the sinus broke down again, and on October 3 he was once more hospitalized for penicillin therapy. He was given 50,000 units intramuscularly at once. This was followed by an injection of 5,000 units into one sinus, while the balance was administered intramuscularly in doses of 10,000 units every three hours. Although the leg looked better after this treatment, the discharge had recurred by the end of the month. Additional laboratory studies were carried out, and it was found that the organisms remained susceptible to penicillin. On December 17 the patient was readmitted to the hospital, and this time he received penicillin with Tergitol as follows: 100,000 units of penicillin was dissolved in 25 cc. of 0.1 per cent solution of Tergitol and 1 cc. of this solution put into the sinus tract every three hours until a total of 500,000 units had been used. A small petrolatum dam was placed around the sinus in order that any overflow of the solution would form a pool, thereby insuring constant contact with penicillin.

The sinus tract healed rapidly after this therapy was instituted and has remained well ever since. This time has now (March 8, 1945) amounted to nine weeks and six days; the patient states that previously he had not been free from the purulent discharge for longer than a two week period.

Case 2.—In a woman, aged 51 years, with hypertensive heart disease, auricular fibrillation developed in October 1944. On November 1 she had a cerebral embolus with temporary hemiplegia and was hospitalized immediately. This was followed on November 9 with a saddle embolis of the aorta. Intensive therapy failed to prevent gangrene of the right leg, and a right midthigh amputation was carried out with local anesthesia on November 15. Although the blood supply of the stump was not entirely adequate, it was deemed unwise to attempt more extensive surgical procedures at that time.

She had a stormy convalescence; her temperature did not reach a normal level, and the amputation stump became necrotic in appearance, showing poor vitality accentuated by the limited blood supply. A culture revealed Bacillus coli, Staph. aureus, Staph. albus, beta streptococci and gamma streptococci. On the ninth postoperative day the suppurative character of the wound failed to show improvement and two Dakin tubes were inserted into the stump under the open skin flaps. Every three hours 100 cc. of solution made up of 200,000 units of penicillin dissolved in 2,000 cc. of sterile isotonic solution of sodium chloride with 50 cc. of 0.2 per cent Tergitol was placed in the tubes. This was continued until 2,000 cc. of the solution had been used. The general appearance of soft tissue parts about the wound improved.

On the fourteenth postoperative day a débridement of the stump was done with the patient under general anesthesia (cyclopropane) and about 6 cm. of protruding necrotic femur was removed. After this procedure the dosage of penicillin was repeated as before, for a total dose of 400,000 units. The wound took on a healthy appearance; the patient made an uneventful recovery and was discharged from the hospital on Jan. 18, 1945.

Case 3.—An unmarried woman, aged 18 years, was first seen on Nov. 23, 1943, complaining of intermittent drainage and induration of the left leg above the knee for a period of ten years. Her history was as follows: Ten years previously she had had measles with subsequent pleurisy and fever. At the same time severe pain in the distal portion of the left thigh developed. She was hospitalized for a period of fourteen months; sequestrectomy of the left femur was done, followed by curettage, and the extremity was immobilized in a cast. From August 1935 through August 1936 she was rehospitalized on six occasions; saucerization of the left femur was done, and numerous casts were applied. This patient has had sixteen operations and has been under good surgical supervision.

Examination here revealed tonsillar and dental sepsis. The left leg was atrophic, grade III (basis IV) with 2 inch (5 cm.) shortening. There were multiple scars on both the inner and the outer aspect of the thigh just above the knee, with dense scar tissue and pronounced contraction.

The patient cooperated by having a tonsillectomy and extraction of an abscessed tooth at once. She then reported gradual improvement until March 1944, when bursitis of the left knee developed after a fall. Additional dental studies at this time demonstrated a devitalized tooth, but, contrary to advice, she delayed having it extracted for nearly five months (July), until she noted soreness about the site of the old incisions on the left leg. After extraction of this tooth, which was reported to have been badly diseased, the soreness and swelling gradually subsided and she had no

15. Furlong, R., and Clark, J. M. P.: On the Use of Penicillin to Control Infection in Open Fractures, Brit. J. Surg. (supp.) **32**:147 (July) 1944.

complaints until Nov. 20, 1944, when she reported fever (temperature of 100 F.), malaise and anorexia combined with swelling of the left leg on the inner aspect over the distal portion of the femur; the lower portion of the leg was painful on the outer aspect. The leg was red and warm; there was definite limitation of motion.

She was hospitalized immediately for penicillin therapy and received, over a period of eight days, 365,000 units; 50,000 units combined with 12 cc. of 0.1 per cent Tergitol was injected locally at once and forty-eight hours later a second dose, of 45,000 units in 11 cc. of 0.1 per cent Tergitol, was injected. The rest, 270,000 units, was given intramuscularly, 10,000 units every four hours. She was discharged from the hospital on November 29, and was then followed at the clinic. We continued the topical application of penicillin until Jan. 4, 1945, at which time she had received 130,000 additional units, a total of 500,000 units. The remainder of the penicillin was administered in the following manner:

Date	Dosage
Dec. 4, 1944	8 cc. of solution made by dissolving 100,000 units of penicillin in 20 cc. of 0.1 per cent Tergitol was injected into the lower, outer aspect of the scar on the left leg.
Dec. 7, 1944	10 cc. of solution of same concentration injected in like manner.
Dec. 11, 1944	5 cc. of solution of same concentration injected in like manner.
Dec. 18, 1944	A new solution, 200,000 units of penicillin dissolved in 25 cc. of 0.1 per cent Tergitol, was prepared and 2 cc. of this concentration injected.
Dec. 19, 1944	3 cc. of the same concentration was injected.
Dec. 21, 1944	3 cc. of the same concentration was injected.
Dec. 28, 1944	3 cc. of the same concentration was injected.
Jan. 2, 1945	3 cc. of the same concentration was injected.
Jan. 4, 1945	3 cc. of the same concentration was injected.

In the past either such local attacks of swelling and pain had resolved themselves by breaking down and discharging or the swelling would persist for many months. After topical injection of penicillin, the swelling subsided at once. With all focal infection apparently removed before the last episode, we feel that this latent infection in the bone may have been the last focus and that the local injection of Tergitol and penicillin might eliminate it permanently.

CONCLUSION

The available evidence suggests that topically applied penicillin containing 500 Oxford units per cubic centimeter may not be sufficiently concentrated for optimum therapeutic effect in refractory chronic infections. Present pharmacologic purity and possible risk of establishing resistant strains of bacteria by selection justify an upward revision of concentration. We found definite advantages in the use of 4,000 units per cubic centimeter in isotonic solution of sodium chloride with 0.1 per cent of the detergent sodium tetradecyl sulfate for local application to chronically infected areas of bone and soft tissue, and for the treatment of infected amputations. If experience in a larger number of cases confirms the efficacy of this simple procedure, it is possible that the magnitude of mutilating major surgical procedures for osteomyelitis may be substantially limited.